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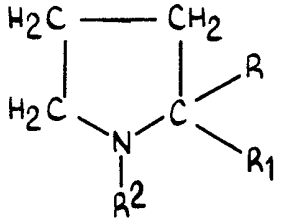
(54) 2-BENZYLPYRROLIDINES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(71) We, BYK GULDEN LOMBERG CHEMISCHE FABRIK GESELLSCHAFT MIT BESCHRANKTER HAFTUNG, a German Company, of Byk-Gulden-Straße 2, D-7750 Konstanz, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to 2-benzylpyrrolidines which are substituted one or more times in the phenyl ring, a process for their preparation, and to medicaments containing them.

In German Patent Specification 1,049,380 [Chem. Abstr. 55 (1961) P4532c] there is described a process for the preparation of α-substituted pyrrolidines of the general formula A



(A)

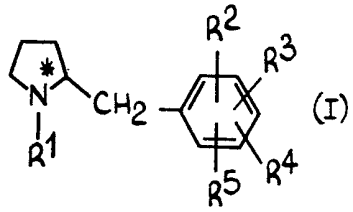
in which

R denotes a hydrogen atom, an alkyl, aryl, aralkyl or heterocyclic radical,
R′ denotes an alkyl, aryl, aralkyl or heterocyclic radical or the cyano group, and
R^2 denotes a hydrogen atom or a monovalent organic radical.

The compounds obtained according to this process are intended to be used as medicaments; no specific action is assigned to them and, as sole compound, α-phenylpyrrolidine is stated by way of example. In the course of their work on the synthesis of nicotine analogues, J. H. Burckhalter and J. H. Short [J org. Chem. 23 (1958) 1281—86] report on, among other things, 2-benzylpyrrolidine and 2 - benzyl - 1 - methylpyrrolidine, and draw attention to the publications of D. F. Starr et al [J. Amer. Chem. Soc. 54 (1932) 3971] and R. Lukes [Chem. Listy 27 (1933) 392, 409, Chem. Abstr 29 (1935) 1720]. 2 - benzyl - i - methylpyrrolidine was, further, obtained in low yield by Fery and van Hove [Bull. Soc. chim. Belg. 69 (1960) 63—78; Chem. Abstr. 55 (1961) 4475d] through re-arrangement of 1 - methyl - 1 - benzylpyrrolidinium iodide. Within the scope of their work on the re-arrangement of α-aminoketones during the Clemmensen reduction. N. J. Leonard

et al. [J. Amer. Chem. Soc. 75 (1953) 3727—30] describe the preparation of 1 - ethyl - 2 - benzylpyrrolidine without stating a pharmacological activity for the latter substance. 2-benzylpyrrolidine showed no activity in regard to hypertension caused by adrenalin; 2 - benzyl - 1 - methylpyrrolidine caused merely a partial reduction of hypertension induced by adrenalin. Accordingly, the last-mentioned compounds are not, or are only to a very limited extent, capable of being used as anti-hypertensive agents. In German Offenlegungsschrift (Published Specification) 25,48,053 [Derwent, Pharmdoc Basic Number 36351X/20], saturated α-substituted benzyl - 1 - benzhydrylazaheterocyclic compounds, in particular α-substituted benzyl - 1 - benzhydrylazetidines, are described which are intended to serve for the treatment of obesity.

The subject matter of the invention is substituted 2-benzylpyrrolidines of the general formula I



wherein

R^1 denotes a hydrogen atom, a straight-chain or branched aliphatic or alicyclic hydrocarbon radical, a cycloalkylalkyl group or an optionally substituted aralkyl or aroylalkyl group,

R^2 denotes a halogen atom, an alkyl group, a hydroxyl group, an alkoxy group, an acyloxy group, an amino group which may be substituted, a nitro group, or a phenyl group which may be substituted,

R^3, R^4 and R^5 are the same or different and denote a hydrogen atom, a halogen atom, an alkyl group, a hydroxyl group, an alkoxy group, an acyloxy group, an optionally substituted amino group, a nitro group, or an optionally substituted phenyl group,

their quaternary alkylpyrrolidinium compounds and their acid addition salts.

Suitable as aliphatic hydrocarbon radicals are straight-chain or branched alkyl radicals with 1 to 7 carbon atoms. Straight-chain alkyl radicals are the methyl, ethyl, propyl, butyl, pentyl, hexyl or heptyl radical, of which those with 1 to 5, in particular 1 to 3, above all 1 to 2, carbon atoms are preferred. Branched alkyl radicals with 3 to 7 carbon atoms are e.g. the isopropyl, sec.-butyl, tert.-butyl, the 3-methylbutyl, the 2,2-dimethylpropyl, the 2-methylpentyl, the 3,3-dimethylbutyl or the 2 - ethyl - 3 - methylbutyl radical, of which those with 3 to 5, above all with 3 to 4, carbon atoms are preferred. Suitable as alicyclic hydrocarbon radicals are cycloalkyl radicals with 3 to 7 carbon atoms, for example the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl radical, of which those with 5 to 6 carbon atoms are preferred.

Suitable as cycloalkylalkyl groups are those with 1 to 4 carbon atoms in the alkyl radical and 3 to 7 carbon atoms in the cycloalkyl radical, of which those with 1 to 2 carbon atoms in the alkyl radical and 3 to 5 carbon atoms in the cycloalkyl radical are preferred. Selected cycloalkylalkyl groups are the cyclopropylmethyl and the cyclobutylmethyl group.

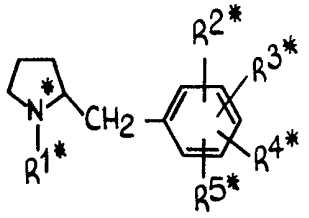
Suitable as aralkyl groups are those with aryl groups which contain up to 12 carbon atoms, and alkyl groups which contain 1 to 4 carbon atoms, of which those with 6 carbon atoms in the aryl radical and 1 to 4 carbon atoms in the alkyl radical, above all with 1 carbon atom in the alkyl radical, are preferred. Mentioned by way of example are the benzyl, phenethyl and phenylpropyl group, of which the benzyl group is preferred. The aralkyl groups may also be substituted, of which those preferred are monosubstituted in the aryl radical by, among other things, halogen atoms, such as fluorine, chlorine or bromine atoms, alkyl and/or alkoxy groups with 1 to 4 carbon atoms. Mentioned for example are the p-chlorobenzyl, the m-chlorobenzyl, the p-bromobenzyl, the o-fluorobenzyl, the p-fluorobenzyl, the p-tolyl and the p-methoxybenzyl group. Among the aralkyl or aroylalkyl groups substituted in the alkyl group, the arylhydroxyalkyl and, in particular, the aryloxoalkyl groups are preferred; mentioned for example are the benzoylmethyl, 2-benzoylethyl, 3-benzoylpropyl, preferably the 3 - (p - chlorobenzoyl) - propyl, in particular the 3 - (p - fluorobenzoyl) - propyl group.

Suitable as halogen atoms R^2, R^3, R^4 or R^5 are fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine, bromine, in particular chlorine. Mentioned as alkyl group or alkoxy groups R^2, R^3, R^4 or R^5 are, *inter alia*, those with 1 to 4 carbon atoms, of which those with 1 to 3, above all those with 1 carbon atom(s), are preferred. Suitable as acyloxy groups are, *inter alia*, —O—CO—R^1 groups in which R^1 has the meaning stated above, of which the alkanoyloxy group with 1 to 7, in particular with 2 to 5, carbon atoms, above all the acetoxy group, are preferred. Besides the unsubstituted amino group, also suitable as substituents R^2, R^3, R^4 or R^5 are substituted amino groups, of which there are mentioned for example alkylamino and dialkylamino groups with 1 to 4, preferably 1 or 2 carbon atoms in the alkyl radical as well as acylamino groups with the usual groups employed for the protection of amino groups, such as alkanoyl groups with 2 to 5 carbon atoms. Suitable as substituents R^2, R^3, R^4 or R^5 are, besides the unsubstituted phenyl group, phenyl groups substituted by halogen atoms, hydroxyl, alkyl and/or alkoxy groups with 1 to 4 carbon atoms, of which the p-substituted phenyl groups, such as the p-chlorophenyl, the p-fluorophenyl, the p-hydroxyphenyl, the p-methoxyphenyl group are preferred.

Suitable as quaternary alkylpyrrolidinium compounds are, *inter alia*, the alkylpyrrolidinium hydroxides; halides, for example iodides, bromides, chlorides; sulphonates, for example p-toluenesulphonates; sulphates, for example methylsulphates, the alkyl radical having in general 1 to 7 carbon atoms. Preferred alkylpyrrolidinium compounds are the alkylpyrrolidinium iodides in which the alkyl radical has up to 4 carbon atoms, in particular 1 carbon atom.

As salts, all acid addition salts are suitable. Particularly mentioned are the pharmacologically compatible salts of the inorganic and organic acids usually employed in Galenic practice. Pharmacologically incompatible salts are converted into pharmacologically compatible salts by processes known to one skilled in the art. Suitable as such are for example water-soluble and water-insoluble acid addition salts, such as the hydrochloride, hydrobromide, hydriodide, phosphate, nitrate, sulphate, acetate, citrate, gluconate, benzoate, hibenzate (2 - (4 - hydroxybenzoyl) - benzoate), fendizoate (o - [2' - hydroxy - 4 - biphenylyl) - carbonyl] - benzoate), propionate, butyrate, sulphosalicylate, maleate, malate, fumarate, succinate, oxalate, tartrate, amsonate (4,4' - diamino - stilbene - 2,2' - disulphonate), embonate (1,1' - methylene - bis - 2 - hydroxy - 3 - naphthoate), metembonate, stearate, tosilate (p-toluenesulphonate), 2 - hydroxy - 3 - naphthoate, 3 - hydroxy - 2 - naphthoate, mesilate (methanesulphonate); further, salts with bumetanide (3 - (butylamino) - 4 - phenoxy - 5 - sulphamoyl - benzoic acid), furosemide (4 - chloro - N - furfuryl - 5 - sulphamoylanthranilic acid), besunide (4 - benzyl - 3 - (butylamino) - 5 - sulphamoylbenzoic acid), piretanide (4 - phenoxy - 3 - (1 - pyrrolidinyl) - 5 - sulphamoylbenzoic acid), etacrynic acid ([2,3 - dichloro - 4 - (2 - methylenebutyryl) - phenoxy] - acetic acid), tienilinic acid ([2,3 - dichloro - 4 - (2 - thenoyl) - phenoxy] - acetic acid).

One embodiment of the invention is substituted 2-benzylpyrrolidines of the general formula I*



(I*)

wherein

R^{1*} denotes a hydrogen atom, a straight-chain or branched aliphatic hydrocarbon radical with 1 to 5 carbon atoms, a cycloalkylalkyl group with 1 or 2 carbon atoms in the alkyl radical and 3 to 5 carbon atoms in the cycloalkyl radical, or an optionally mono-substituted phenylalkyl group with 1 to 4 carbon atoms in the alkyl radical,

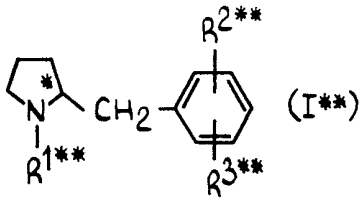
R^{2*} denotes a halogen atom, a hydroxyl group, an alkyl group with 1 to 4 carbon atoms, an alkoxy group with 1 to 4 carbon atoms, an alkanoyloxy group with 2 to 5 carbon atoms, an amino group, a dialkylamino group with 1 or 2 carbon atoms per alkyl radical or a nitro group or a phenyl group which may be substituted in p-position,

R^{3*}, R^{4*} and R^{5*} independently of one another denote a hydrogen atom, a

halogen atom, a hydroxyl group, an alkyl group with 1 to 4 carbon atoms, an alkoxy group with 1 to 4 carbon atoms, an alkanoyloxy group with 2 to 5 carbon atoms, an amino group, a dialkylamino group with 1 or 2 carbon atoms per alkyl radical or a nitro group, and at least one of the substituents in 2- or 6-position of the benzyl group is a hydrogen atom, their quaternary (C_1—C_4) alkylpyrrolidinium compounds and their pharmacologically compatible acid addition salts.

A further embodiment of the invention is those 2-benzylpyrrolidines of the general formula I* in which R^{1*}, R^{2*}, R^{3*}, R^{4*} and R^{5*} have the meaning stated above, and at least one, preferably two, of the substituents R^{3*}, R^{4*} or R^{5*} and at least one of the substituents in 2- or 6-position of the benzyl group denote a hydrogen atom, and their quaternary (C_1—C_4) alkylpyrrolidinium compounds and their pharmacologically compatible acid addition salts.

Preferred substituted 2-benzylpyrrolidines are those of the general formula I**



(I**)

wherein

R^{1**} denotes a hydrogen atom, a straight-chain alkyl radical with 1 to 3 carbon atoms, a branched alkyl radical with 3 to 5 carbon atoms, a cycloalkylmethyl radical with 3 to 5 carbon atoms in the cycloalkyl group or a benzyl radical which may be substituted in p-position by halogen, methyl or methoxy,

R^{2**} denotes a halogen atom, a hydroxyl group, a methoxy group, an amino group or a nitro group,

R^{3**} denotes a hydrogen atom, a halogen atom, a hydroxyl group, a methoxy group, an amino group or a nitro group, the substituents R^{2**} and R^{3**} preferably being in 2-, 3- and/or 4-position,

and their methylpyrrolidinium compounds and their pharmacologically compatible acid addition salts.

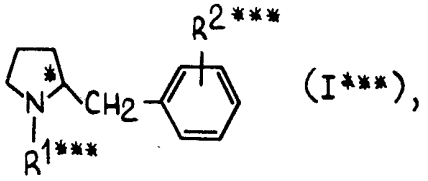
Selected substituted 2-benzylpyrrolidines of the formula I** are those in which

R^{1**} denotes a hydrogen atom, a methyl group, an isopropyl group, a tert.-butyl group, a cyclopropylmethyl group or a benzyl group,

R^{2**} and R^{3**} have the meaning stated above,

and their pharmacologically compatible acid addition salts.

Particularly preferred substituted 2-benzylpyrrolidines are those of the formula I***



(I***),

wherein

R^{1***} denotes a hydrogen atom, a methyl group, an isopropyl group or a cyclopropylmethyl group, and

R^{2***} denotes a 2-, preferably 3- or 4-positioned fluorine, chlorine, hydroxy, methoxy or amino substituent,

and their pharmacologically compatible acid addition salts.

Selected compounds according to the invention are

2 - (2 - chlorobenzyl) - 1 - methylpyrrolidine
2 - (4 - chlorobenzyl) - 1 - methylpyrrolidine
2 - (3 - methoxybenzyl) - 1 - methylpyrrolidine
2 - (3 - hydroxybenzyl) - 1 - methylpyrrolidine
2 - (3 - chlorobenzyl) - 1 - methylpyrrolidine

2 - (2 - methoxybenzyl) - 1 - methylpyrrolidine, in particular
2 - (4 - aminobenzyl) - 1 - methylpyrrolidine, and
2 - (4 - chlorobenzyl) - pyrrolidine,

and their pharmacologically compatible acid addition salts.

The substituted 2-benzylpyrrolidines of the general formula I or I*, I** and I*** possess at the carbon atom characterised by (*) a chirality centre. The invention therefore includes both the racemates and the enantiomers and their mixtures.

The substituted 2-benzylpyrrolidines of the general formula I or of the embodiments I*, I** and I*** and the corresponding alkylpyrrolidinium compounds and the pharmacologically compatible salts possess valuable properties which render them commercially exploitable. In the first place, the compounds, 2-benzylpyrrolidine and the 2 - benzyl - 1 - alkylpyrrolidines, the corresponding alkylpyrrolidinium compounds and the pharmacologically, i.e. biologically, compatible salts have distinct pharmacological properties; in particular, effects on the central nervous system (=CNS), on blood pressure and on sensation of pain and, secondly, they can be converted into other substituted 2-benzylpyrrolidines of the general formula I and therefore represent valuable intermediates for the preparation of pharmacologically active compounds of the general formula I or of the embodiments I*, I** and I*** and of their alkylpyrrolidinium compounds and their pharmacologically compatible salts.

The CNS effectiveness of the 2-benzylpyrrolidines, the alkylpyrrolidinium compounds and the pharmacologically compatible salts extends to central stimulation, increased vigilance, the promotion of normal and pathologically inhibited drive. In addition, some representatives exhibit a strong analgesic effect or an action which influences the blood pressure.

The excellent and broad pharmacological effectiveness of the 2-benzylpyrrolidines enables their use both in human and in veterinary medicine; they may be used for prophylaxis before symptoms or for the treatment of symptoms which have already occurred.

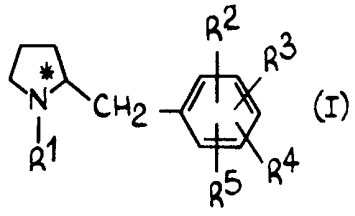
As indications for the human medical ranges in men and in women there are mentioned lack of drive, reduced vigilance, depression, organic psychosyndromes in the case of cerebral retrogression processes, lack of vitality, blood-pressure troubles and exhaustion states as well as pain states; in children, inhibition of mental and psychological development as well as difficulties in learning.

In the field of veterinary medicine, the indications are reduced vitality and pain states. For example, higher animals, such as economically useful animals and domestic animals, can be treated.

The compounds of the general formula I exhibit, depending on the nature of the substitution pattern, an activity spectrum with various focal points, one of the aforesaid actions being emphasised, in particular the central stimulating activity, as for example in the case of 2 - (3 - methoxybenzyl) - 1 - methylpyrrolidine, or the analgesic effect, as for example in the case of 2 - (2 - methoxybenzyl) - 1 - methylpyrrolidine, or the effect which influences blood pressure, as for example in the case of 2 - (2 - chlorobenzyl) - 1 - methylpyrrolidine and 2 - (3,4 - dihydroxybenzyl) - 1 - methylpyrrolidine; or a combination of these effects is emphasised, as for example the analgesic and central-stimulating activity, for example in the case of 2 - (4 - chlorobenzyl) - pyrrolidine, 2 - (4 - chlorobenzyl) - 1 - methylpyrrolidine, 2 - (4 - chlorobenzyl) - 1 - isopropylpyrrolidine or 2 - (4 - aminobenzyl) - 1 - methylpyrrolidine, or the effect which stimulates centrally and influences the blood pressure, as for example in the case of 2 - (3 - hydroxybenzyl) - 1 - methylpyrrolidine.

Depending on the desired therapeutic objective, one or more of the said 2-benzylpyrrolidines of the appropriate type of activity is/are used.

The invention also relates to medicaments which contain the 2-benzylpyrrolidines of the general formula I



wherein

R^1 denotes a hydrogen atom, a straight-chain or branched aliphatic or alicyclic hydrocarbon radical, a cycloalkylalkyl group or an aralkyl group,

R^2, R^3, R^4 and R^5 are the same or different and denote a hydrogen atom, a halogen atom, an alkyl group, a hydroxyl group, an alkoxy group, an acyloxy group, an optionally substituted amino group, a nitro group, or an optionally substituted phenyl group,

their quaternary alkylpyrrolidinium compounds and/or their pharmacologically compatible acid addition salts.

Preferred medicaments are those which contain substituted benzylpyrrolidines of the embodiments I*, I**, I*** or the corresponding alkylpyrrolidinium compounds and/or the pharmacologically compatible acid addition salts.

The medicaments are prepared according to methods which are known per se. As medicaments, the new compounds may be used as such or, where appropriate, in combination with suitable pharmaceutical excipients. When the new pharmaceutical preparations contain pharmaceutical excipients besides the active substances, the active substance content of these mixtures is 5 to 95, preferably 25 to 75, per cent by weight of the total mixture.

In agreement with the invention, in the human and veterinary medical field the active substances may be used in any desired form, e.g. systemically or topically, provided that the formation and maintenance of sufficient blood or tissue levels or local concentrations of 2-benzylpyrrolidines is ensured. This may be achieved either by oral, rectal or parenteral administration in suitable doses. The new medicaments may, however, also be applied locally. Advantageously, the pharmaceutical preparation of the active substance is in the form of unit doses which are matched to the desired administration. A unit dose may for example be a tablet, a dragee, a capsule, a suppository or a measured volume amount of a powder, a granulate, a solution, an emulsion, a suspension, a sol or a gel.

By "unit dose" in the sense of the present invention is understood a physically specified unit which contains an individual amount of the active constituent in combination with a pharmaceutical excipient, the active substance content of which specified unit corresponds to a fraction of, or to a multiple of, a therapeutic individual dose. An individual dose contains preferably the amount of active substance which is administered at one application and which normally corresponds to a whole, a half, a third or a quarter of the daily dose. When only a fraction, such as the half or a quarter, of the unit dose is needed for an individual therapeutic administration, the unit dose is advantageously divisible, e.g. in the form of a tablet with break score.

The pharmaceutical preparations according to the invention contain, when they are present in unit doses and are intended for application e.g. to humans, 1 to 200 mg, advantageously 2.5 to 100 mg and, in particular, 5 to 50 mg of active substance.

In general, it has proved advantageous both in human and in veterinary medicine to administer the active substance or substances, in the case of oral administration, in a daily dose of 0.06 to 12, preferably 0.14 to 5.7, in particular 0.3 to 3 mg/kg body weight, where appropriate in the form of several, preferably 1 to 3, individual administrations, in order to achieve the desired results. One individual administration contains the active substance or substances in amounts of 0.01 to 3.0, preferably 0.04 to 1.5, in particular 0.07 to 0.7 mg/kg body weight.

In the case of a parenteral treatment, e.g. in the case of an acute depression or a severe pain state, similar dosages may be applied. In this therapy, 1 to 50 mg of active substance are applied.

For a local application, preparations in pharmacologically compatible, e.g. aqueous, solution are suitable which contain 0.1 to 5, preferably 0.2 to 3, in particular 0.5 to 2 per cent by weight of active substance.

The therapeutic administration of the pharmaceutical preparation, in the case of long-term medication, is in general effected at fixed points-in-time, such as 1 to 4 times daily, e.g. in each case after meals and/or in the evening. In acute cases, medication occurs at a varying point-in-time. Under certain circumstances it may be necessary to deviate from the said dosages, depending on the nature, the body weight and the age of the subject to be treated, the nature and gravity of the illness, the nature of the preparation and the application of the medicament as well as the space of time or interval within which the administration occurs. Thus, it may in some cases suffice to manage with less than the above-mentioned amount of active substance, whereas in other cases the above-mentioned amount of active substance

must be exceeded. The establishing of the optimum dosage and type of application of active substances required in each case can at any time be effected by the skilled man on the basis of his specialised knowledge.

The pharmaceutical preparations consist as a rule of the active substances according to the invention and non-toxic, pharmaceutically compatible medicament excipients which are used as additive or diluent in solid, semi-solid or liquid form or as surrounding agent, for example in the form of a capsule, a tablet coating, a bag or other container for the therapeutically active constituent. An excipient may serve e.g. as medium for absorption of the medicament by the body, as formulation auxiliary, as sweetener, as taste corrector, as colouring matter or as preservative.

For oral application e.g. tablets, dragees, hard and soft capsules, e.g. of gelatin, dispersible powders, granulates, aqueous and oily suspensions, emulsions, solutions or syrups may be used.

Tablets may contain inert diluents, e.g. calcium carbonate, calcium phosphate, sodium phosphate or lactose; granulation and distribution agents, e.g. maize starch or alginates; binders, e.g. starch, gelatin or acacia gum; and lubricants, e.g. aluminium stearate or magnesium stearate, talc or silicone oil. They may additionally be provided with a coating which may also be of such a nature that a delayed dissolution and resorption of the medicament in the gastro-intestinal tract and, thus, e.g. a better compatibility, protraction or a retardation is achieved. Gelatin capsules may contain the medicament mixed with a solid diluent, e.g. calcium carbonate or kaolin, or an oily diluent, e.g. olive oil, arachis oil or paraffin oil.

Aqueous suspensions may contain suspending agents, e.g. sodium carboxymethylcellulose, methylcellulose, hydroxypropylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth or acacia gum; dispersing and wetting agents, e.g. polyoxyethylene stearate, heptadecaethyleneoxycetanol, polyoxyethylenesorbitol mono-oleate, polyoxyethylenesorbitan mono-oleate or lecithin; preservatives, e.g. methyl or propyl hydroxybenzoates; flavourings; sweeteners, e.g. sucrose, lactose, sodium cyclamate, dextrose, invert sugar syrup.

Oily suspensions may contain e.g. arachis, olive, sesame, coconut or paraffin oil and thickeners, such as e.g. beeswax, hard paraffin or cetyl alcohol; further, sweeteners, flavourings and anti-oxidants.

Powders and granulates dispersible in water may contain the medicaments mixed with dispersing, wetting and suspending agents, e.g. those mentioned above, and sweeteners, flavourings and colouring matter.

Emulsions may contain e.g. olive, arachis or paraffin oil besides emulsifiers, such as e.g. acacia gum, gum tragacanth, phosphatides, sorbitan mono-oleate, polyoxyethylenesorbitan mono-oleate, and sweeteners and flavourings.

For rectal application of the medicaments, suppositories are used which are produced with the aid of binders which melt at rectal temperature, for example cocoa butter or polyethyleneglycols.

For parenteral application of the medicaments, there can be used sterilely-injectable aqueous suspensions, isotonic salt solutions or other solutions which may contain dispersing or wetting agents and/or pharmacologically compatible diluents, e.g. propyleneglycol or butyleneglycol.

Gels, sols or tablets suitable for local treatment may contain, besides the active substance or substances, the usual excipients, e.g. animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethyleneglycols, silicones bentonites, silicic acid, talc and zinc oxide or mixtures of these substances.

Powders and sprays may contain, besides the active substance or substances, the usual excipients, e.g. lactose, talc, silicic acid, aluminium hydroxide, calcium silicate and polyamide powder or mixtures of these substances. Sprays may, in addition, contain the usual propellants, e.g. chlorofluorohydrocarbons.

The active substance or substances, where appropriate with one or more of the above-mentioned excipients, may also be present in microencapsulated form.

Besides the 2-benzylpyrrolidines, the pharmaceutical preparations may contain for example one or more pharmacologically active constituents from other groups of medicaments, for example mild stimulants, such as caffeine; analgesics, such as aminophenazone, acetylsalicyclic acid, d-propoxyphen; antidepressants, dibenzepin, dioxepin maprotiline, amitripyltine, nortryptiline, melitracen, tranquilizers, such as benzodiazepines, e.g. diazepane, chlorodiazepoxide, meprobamate, agents which promote cerebral blood circulation and/or tonics, such as glutamic acid, vitamins or combinations thereof.

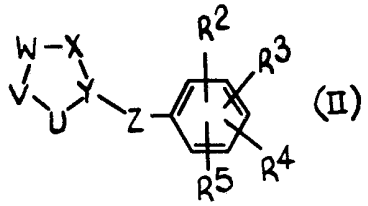
Mammals which are suffering from primary or secondary disturbances of the central nervous system or from pathological changes of blood pressure or from pain states may be treated by a process which is characterised in that there is administered to the mammal affected a CNS-effective or blood-pressure-influencing or analgesic and pharmacologically compatible amount of one or more 2-benzylpyrrolidines and/or their pharmacologically compatible salts.

The intermediates of the general formula I or of the embodiments I*, I** or I*** can be converted according to known methods into pharmacologically active compounds of the general formula I, as is described in the following Examples. Thus, for example there are obtained from the free bases the acid addition salts by reaction with the appropriate acid, and the alkylpyrrolidinium compounds are obtained through reaction with the appropriate alkyl halides or alkylsulphonates. Ethers, i.e. compounds in which one or more of the substituents R^2, R^3, R^4, R^5 represent an alkoxy group are converted into the free hydroxy compounds through acid hydrolysis, e.g. with halogen hydride. Esters, i.e. compounds in which one or more of the substituents R^2, R^3, R^4, R^5 represent an acyloxy group, are converted into the free hydroxy compounds by alkaline hydrolysis, e.g. with sodium hydroxide. The free hydroxy compounds, i.e. those in which one or more of the substituents R^2, R^3, R^4, R^5 represent an OH group, may be etherified or esterified.

Some intermediates are likewise pharmacologically active; e.g. the nitriles IX and their N-alkyl, N-cycloalkyl, N-cycloalkylalkyl and N-aralkyl derivatives are distinguished by an analgesic action with lox toxicity. They may therefore be used as analgesics; the dose to be administered, the administration and application correspond to the above-mentioned range.

The invention further relates to a process for the preparation of the substituted 2-benzylpyrrolidines of the general formula I, which process is characterised in that

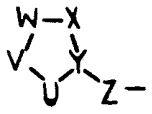
(a) a substituted 2-benzylpyrrolidine of the general formula II



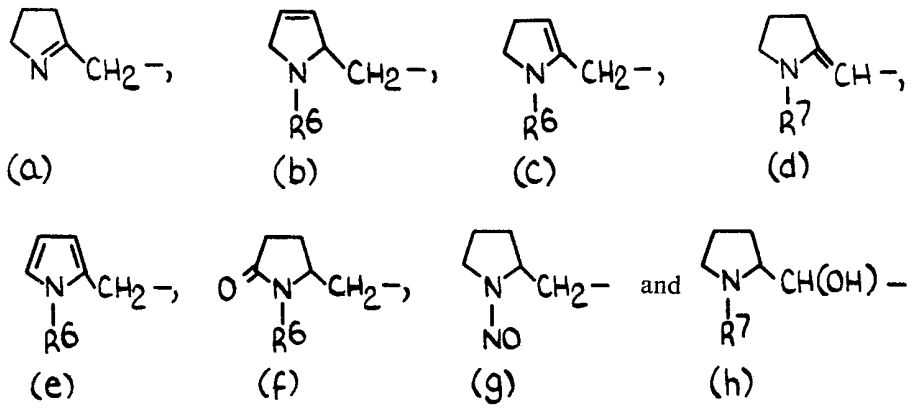
(II)

wherein

R^2, R^3, R^4 and R^5 have the meaning stated above and



denotes one of the groupings



wherein

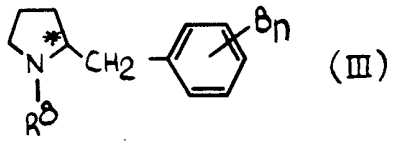
R^6 represents a hydrogen atom, a straight-chain or branched aliphatic or

alicyclic hydrocarbon radical, a cycloalkylalkyl radical or an optionally substituted aralkyl or aroylalkyl group, and

R^7 represents a straight-chain or branched aliphatic or alicyclic hydrocarbon radical, a cycloalkylalkyl radical or an optionally substituted aralkyl or aroylalkyl group,

is reduced and, where appropriate, subsequently N-alkylated or N-debenzylated and/or functionalised and/or the free base obtained or its acid addition salts are converted into one another in the usual manner or

(b) a 2-benzylpyrrolidine of the general formula III



(III)

wherein

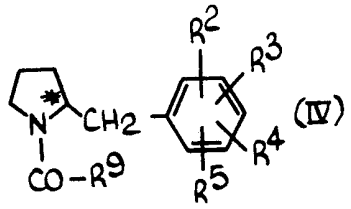
R^8 denotes a hydrogen atom, a straight-chain or branched aliphatic or alicyclic hydrocarbon radical or a cycloalkylalkyl radical,

B denotes a hydrogen atom or a precursor of a functional group, and

n denotes a whole number from 1 to 4, preferably 1 to 2, in particular 1,

is functionalised as herein defined and, where appropriate, subsequently N-alkylated or N-debenzylated and/or the obtained free base or its acid addition salts are converted into one another in the usual manner or

(c) an N-acyl-2-benzylpyrrolidine of the general formula IV



(IV)

wherein

R^2, R^3, R^4 and R^5 are the same or different and denote a hydrogen atom, a halogen atom, an alkyl group, a hydroxyl group, an alkoxy group, an optionally substituted amino group, or an optionally substituted phenyl group,

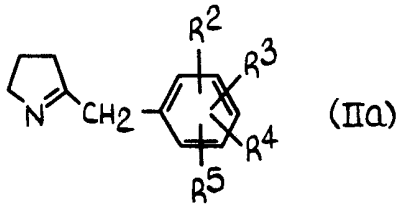
R^9 denotes a straight-chain or branched aliphatic or alicyclic hydrocarbon radical, a cycloalkylalkyl radical, an optionally substituted phenyl radical or an optionally substituted phenylalkyl radical,

is reduced and, where appropriate, subsequently functionalised and/or N-alkylated or N-debenzylated and/or the base obtained or its acid addition salts are converted into one another in the usual manner.

The reduction of the substituted 2-benzyl-pyrrolidines of the general formula IIa—e and g is effected preferably with hydrogen in organic solvents such as are known to the skilled man for hydrogenation reactions, for example ethanol, methanol, cyclohexane, isopropanol, dimethylformamide, in the presence of metal catalysts, e.g. platinum, platinum on activated charcoal, palladium, palladium on activated charcoal, Raney nickel, at pressures of 1 to 500 atmospheres and temperatures around room temperature, for example 0 to 50°C. The reduction of the compounds of the formula IIa, IIc or IId is effected alternatively in the form of their acid addition salts in aqueous-alcoholic solution with sodium borohydride in manner familiar to the skilled man (cf. "Enamines: Synthesis, Structure and Reactions" edited by A. Gilbert Cook, page 185 ff; Marcel Dekker, New York and London 1969). The reduction of the compounds IIf is effected with lithium aluminium hydride in inert solvents, such as ethers, e.g. diethyl ether, tetrahydrofuran, dioxan, 1,2-dimethoxyethane or diethyleneglycol diethyl ether, at temperatures between 0°C and the boiling temperature of the solvent, preferably between 20°C and 70°C. The reduction of the compounds IIg is alternatively effected by reaction with hydrogen halogenides, preferably hydrogen chloride, in inert solvents, e.g. benzene (cp. Synthesis 1976, 540—541). The reduction of the compounds IIh is effected with hydrogen iodide in preferably polar solvents, such

as acetic acid, water, at temperatures between 80 and 150°C, preferably at the reflux temperature of the solvent, optionally in the presence of red phosphorus.

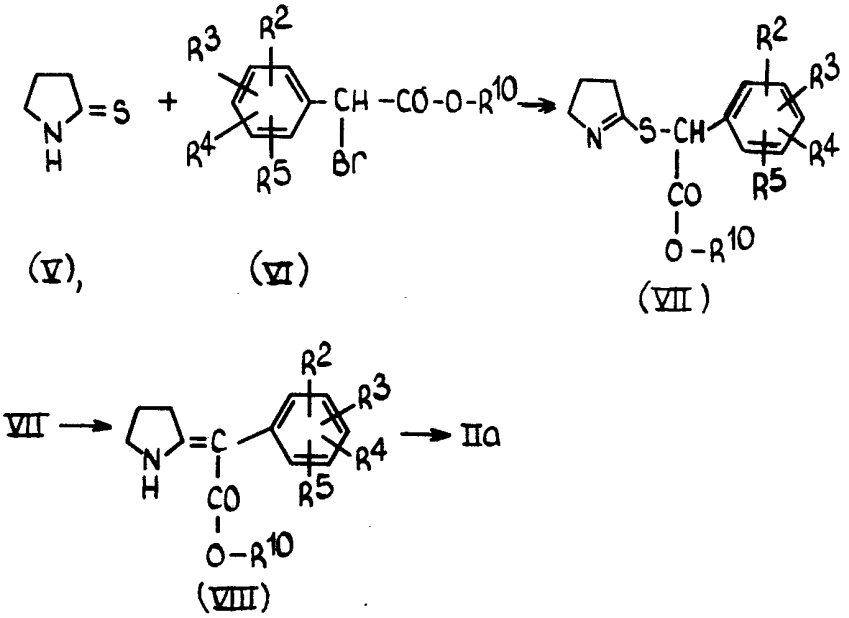
The compounds of the formula IIa to be used as starting compounds



(IIa)

wherein

R^2, R^3, R^4 and R^5 have the meaning stated above, are obtained along the lines of, or according to, processes described in the literature. For example, ω-chlorobutyronitrile is reacted with the appropriately substituted benzylmagnesium halides, preferably those substituted by chlorine and/or alkoxy, in known solvents such as ethers, e.g. diethyl ether, tetrahydrofuran, or aromatic hydrocarbons, e.g. benzene, toluene, xylene, at temperatures between 20 and 160°C, to give the substituted Δ^1-pyrrolines. The compounds of the formula IIa can also be obtained according to I. Felner et al. (Helv. Chim. Acta 53 [1970] 754) or M. Roth et al. (Helv. Chim. Acta 54 [1971] 710) by reaction of 2-thiopyrrolidinone V with appropriately substituted α-bromophenylacetic acid esters VI to give the thiolactim ethers VII, subsequent sulphide concentration to give the enamino esters VIII, hydrolysis and decarboxylation, as is reproduced by the following formula scheme:



(V), (VI) (VII)

(VII) → (VIII) → IIa

in which

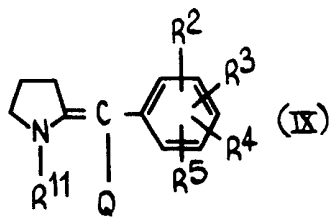
R^2, R^3, R^4 and R^5 have the above meaning and

R^{10} denotes an alkyl radical with 1 to 5 carbon atoms.

Suitable sulphur absorbers are e.g. triphenylphosphine, triethylphosphite, tributylphosphine; for the hydrolysis and subsequent decarboxylation, strong acids, e.g. hydrochloric acid, trifluoroacetic acid, are predominantly used.

The compounds of the general formula IIa can also be prepared in analogy with the process described in German Offenlegungsschrift (Published Specification) 1,470,168 from 2-alkoxy-1-pyrrolines and appropriate benzylmagnesium halides.

The compounds of the formula IIa to be used as starting compounds are also accessible through treatment of the benzylidene compounds IX



(IX)

wherein

R^2, R^3, R^4 and R^5 have the meaning stated above,

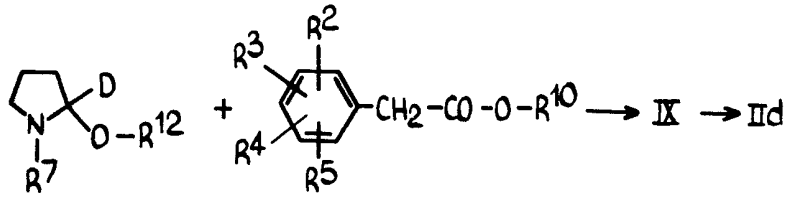
R^{11} represents a hydrogen atom, and

Q represents a CN group,

with strong acids, e.g. with concentrated hydrochloric acid. The benzylidene compounds IX, in which R^{11} represents a hydrogen atom, are accessible for example according to the process described by T. Kametami et al. (J. Chem. Soc., Perkin I *1976*, 389; Heterocycles 3 [1975], 691).

The compounds of the general formula II b) and II c) are prepared in analogy with C. M. Wong et al. (Can. J. Chem. 47 [1969] 2421), M. Salmón et al. C.A. 73 (1970) 14604 u or S. Oida et al. Chem. Pharm. Bull. *17* [1969] 1405. Compounds of the general formula IIb) with R^6 having a meaning different from hydrogen, e.g. a hydrocarbon radical or an aralkyl group, can be obtained by known methods, e.g. by alkylation or aralkylation.

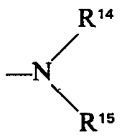
The starting compounds IId) can be prepared according to various processes. For example, they are obtained by reaction of pyrrolidines X with phenylacetic acid esters XI to give the benzylidene compounds IX, hydrolysis and decarboxylation of the latter according to the following reaction scheme



(X) (XI)

wherein

D denotes an —O—R^{13} group or a



group,

R^{11} has the meaning of R^7,

R^{12}, R^{13}, R^{14}, R^{15} are the same or different and denote an alkyl radical with 1 to 5 carbon atoms, preferably a methyl group, and

R^{15} may also denote a cycloalkyl radical with 3 to 6 carbon atoms or a phenyl radical which may be substituted, or

D and O—R^{12} together denote an alkylidenedioxy group with up to 4, preferably 2 carbon atoms,

Q denotes a —CO—O—R^{10} group, and

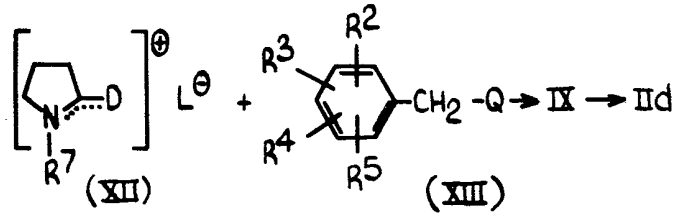
R^2, R^3, R^4, R^5, R^7 and R^{10} have the meaning stated above, in accordance with work by N. P. Kostyuchenko et al. (Khim. Geterotsikl, Soedin, *1974*, 1212). Analogously to the same literature passage, compounds of the formula IId can be obtained from the pyrrolidines X and appropriate phenylacetonitriles via benzylidene compounds IX, in which Q represents a CN group.

The pyrrolidines X are obtained by reacting salts of the formula XII with alkali metal alcoholates, such as sodium methanolate, ethanolate, in suitable solvents [in accordance with H. Bredereck et al. Chem. Ber. 97 (1964) 3081; Chem. Ber. 98

(1965) 1078]. Preferred solvents when prepared pyrrolidines X, in which D denotes an —O—R^{13} group, are alcohols of the formula R^{13}—OH, in which R^{13} has the meaning stated above; preferred solvents when preparing pyrrolidines X in which D denotes a —$NR^{14}R^{15}$ group are inert solvents, such as benzenes and ethers, e.g. diethyl ether.

The reaction of the pyrrolidines X with the acetic acid esters XI or the appropriate acetonitriles is in general carried out at temperatures of 20 to 150°C, preferably between 40 and 100°C, without or preferably with addition of inert organic solvents, such as aliphatic hydrocarbons, e.g. petroleum ether, light petroleum, ligroin, or cycloaliphatic hydrocarbons, e.g. cyclohexane, or aromatic hydrocarbons, e.g. benzene, toluene, xylene. The hydrolysis and simultaneous decarboxylation of the esters or of the appropriate acetonitriles is effected through the action of mineral acids, such as hydrochloric acid, hydrobromic acid, preferably of concentrated hydrochloric acid, at temperatures between room temperature and 120°C, preferably through heating the appropriate solution under reflux until the cessation of evolution of CO_2. The enamines IId) formed from the esters IX or the appropriate acetonitriles are relatively unstable compounds and are in general immediately further processed, that is to say reduced to give the compounds according to the invention. On account of their stability and their ready accessability as well as by reason of the instability of the enamines IId), the esters IX or the appropriate acetonitriles represent interesting and valuable intermediates for the preparation of the 2-benzylpyrrolidines I according to the invention.

The starting compounds IId) are obtained according to a further process through reaction of pyrrolinium salts XII with phenylacetic acid derivatives XIII in the presence of strong bases to give the benzylidene compounds IX and hydrolysis and decarboxylation of the latter according to the following reaction scheme



in which

R^2, R^3, R^4, R^5, R^7 and D have the meaning stated above,

Q represents a CN group or a —CO—O—R^{10} group in which

R^{10} has the meaning stated above,

$L^{\ominus}$ stands for an equivalent of an anion of an organic or inorganic acid.

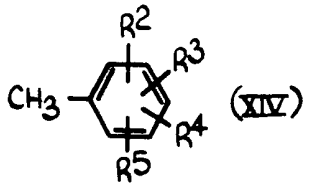
The reaction of the pyrrolinium salts XII with the phenylacetic acid derivatives XIII is in general effected without addition of further solvents in the presence of strong bases, such as solutions of alkali metal alcoholates, for example sodium methanolate, potassium methanolate, potassium propanolate, sodium isopropanolate, potassium butanolate, potassium tert.-butanolate, potassium tert.-pentanolate, in particular sodium ethanolate, at temperatures of 20 to 150°C, preferably 80—100°C. Where appropriate, the reaction is carried out while passing an inert gas through, such as nitrogen, in order to remove the volatile amine which may be formed. The reaction may, however, also be carried out with addition of inert solvents, such as alcohols, for example methanol, ethanol, propanol, isopropanol, butanols, pentanols, such as tert. nitrogen bases, e.g. pyridine, or hydrocarbons, for example benzene. The hydrolysis and decarboxylation of the benzylidene compounds IX are effected analogously to the processes described above.

The preparation of the salts XII is effected for example in analogy with H. Bredereck et al. (Chem. Ber. *1964,* 3081) by reaction of appropriate N-substituted 2-pyrrolidinones with alkylating agents, such as diethyl sulphate, methyl iodide, preferably dimethyl sulphate, in inert sclvents at room temperature up to 120°C, preferably without solvents at temperatures around 80°C, and, when D in the salts XII represents a —$NR^{14}R^{15}$ group, subsequent reaction with the amines $HNR^{14}R^{15}$, or, when D represents a —$NR^{14}R^{15}$ group, through reaction of the appropriate pyrrolidinones with inorganic acid chlorides, such as phosphorus oxy chloride, phosgene, and subsequent reaction with the amines $HNR^{14}R^{15}$, in inert solvents,

such as benzene, at temperatures between 0 and 100°C, preferably 20 to 60°C, or without solvent at temperatures between 0 and 100°C, preferably 40 to 80°C.

The starting compounds IId) are also obtained by reaction of the appropriate 2-pyrrolidinones or their derivatives X with substituted benzylmagnesium halides, preferably disubstituted, in particular monosubstituted, benzylmagnesium chlorides, under the usual reaction conditions of the Grignard synthesis (cf. Houben-Weyl, Vol. 13/20, p. 53 ff.).

The starting compounds IId), in which at least one of the substitutes R^2, R^3, R^4 or R^5 represents a nitro group are further obtained by reaction of the pyrrolidines X with toluenes



(XIV)

in which at least one of the substituents R^2, R^3, R^4 or R^5 represents a nitro group. The reaction is in general effected at temperatures of 20 to 150°C, preferably between 40 and 100°C, without or preferably with addition of inert organic solvents, such as aliphatic hydrocarbons, e.g. petroleum ether, light petroleum, ligroin, or cycloaliphatic hydrocarbons, e.g. cyclohexane, or aromatic hydrocarbons, e.g. benzene, toluene, xylene.

The starting compounds IId), in which at least one of the substituents R^2, R^3, R^4 or R^5 represents a nitro group are also obtained by reaction of the pyrrolinium salts XII with toluenes XIV in which at least one of the substituents R^2, R^3, R^4 or R^5 represents a nitro group, in the presence of strong bases, such as alkali metal alcoholates. Suitable alkali metal alcoholates are for example sodium methanolate, potassium methanolate, potassium propanolate, sodium isopropanolate, potassium butanolate, potassium tert.-butanolate, potassium tert.-pentanolate, in particular sodium ethanolate. The reaction is carried out at temperatures of 20 to 150°C, preferably at 80 to 100°C. Where appropriate, the reaction is carried out while passing an inert gas through, such as nitrogen, in order to remove the volatile amine which may be formed. The reaction is effected either without addition of further solvents or with addition of inert solvents, such as alcohols, for example methanol, ethanol, propanol, isopropanol, butanols, pentanols, such as tertiary nitrogen bases, e.g. pyridine, or hydrocarbons, for example benzene, toluene.

The starting compounds IIe are obtained for example according to the process described in German Offenlegungsschrift 1,470,387, 2-(p-methoxybenzyl)-pyrrole is described in C.A. *63*, 5582g and C.A. *73*, 14604u. 2-(p-chlorobenzoyl)-pyrrole is described in J. Chem. [London] *1964*, 2573, from which 2-(p-chlorobenzyl)-pyrrole is obtained by reduction. Analogously, the other substituted benzylpyrroles IIe) are obtained.

The starting compounds IIf are obtained for example by reaction of the nitriles XIII with succinic acid dialkyl esters, e.g. succinic acid diethyl ester, in the presence of alkali metal alcoholates, e.g. sodium ethanolate, subsequent hydrolysis and decarboxylation analogously to French Patent Specification 1,503,260 to give appropriately substituted phenyl-laevulinic acids, and conversion of the latter into the oxime and amine and subsequent cyclisation analogously to Yakugaku Zasshi 86 (1966) 1212—1216. The thus prepared starting compounds IIf with R^6 denoting a hydrogen atom may, if desired, subsequently be alkylated according to known processes to give compounds IIf with R^6 meaning an alkyl, cycloalkyl, aralkyl or cycloalkylalkyl group.

The starting compounds IIg are obtained for example by lithiation of 1-nitrosopyrrolidine and subsequent reaction with corresponding benzyl halogenides, preferably bromides or iodides, in accordance with the process described in Synthesis 1976, 540—41.

The starting compounds IIh are obtained for example by Grignard reaction of corresponding 2-formyl-pyrrolidines with correspondingly substituted phenyl magnesium halogenides, preferably bromides, and usual working up in accordance with the process described in Tetrahedron Letters 28 (1976) 2437—40. They are obtained alternatively by reduction of correspondingly substituted [pyrrolidinyl-(2)] phenyl ketones with lithium aluminium hydride. The pyrrolidinyl phenyl

ketones are obtained in accordance with the process described in Helv. Chim. Acta 50 (1967) 2520.

The functionalisation of the 2-benzylpyrrolidines III or, where appropriate, the subsequent functionalisation of the substituted benzylpyrrolidines I obtained by reduction, is effected in a manner depending on the nature of the finally desired substituent in the phenyl group as described in the following six paragraphs.

The nitro group is introduced for example by nitration with nitro acid, nitric acid/sulphuric acid, potassium nitrate/sulphuric acid, alkyl nitrate at temperatures of −20 to +50°, preferably −20 to +30°C. In the starting compounds III, B then denotes a hydrogen atom and n=1; in the end products, R^2, R^4 and R^5 denote a hydrogen atom, and R^3 denotes a p-positioned NO_2 group. Under severe conditions, dinitro compounds are formed, i.e. R^4 and R^5 denote a hydrogen atom and R^2 and R^3 denote a nitro group.

The amino group is introduced by reduction of the NO_2 group(s) of an appropriate nitro compound with hydrogen on suitable catalysts, such as Pt; Pt/C, Pd, Pd/C, Raney Ni, in customary solvents, such as alcohols, cyclohexane. In the starting compounds III, B then denotes one or two NO_2 group(s) and n=1 (or 2); in the end products, R^4, R^5 denote a hydrogen atom, and R^2 and/or R^3 denote an NH_2 group.

Halogen atoms, in particular chlorine and bromine atoms, are introduced in the usual manner through nucleus halogenation. Suitable as catalysts for the nucleus halogenation are iron, iron (III) chloride or bromide, aluminium chloride or bromide, tin tetrachloride or iodine; the reaction is carried out without solvents or in inert solvents and, where appropriate, in glacial acetic acid without catalyst, at temperatures between 0 and 20°C.

Hydroxyl groups are introduced through ether splitting of the appropriate alkoxy groups. In the starting compounds III, B then denotes an alkoxy group, preferably a methoxy group, and n=1 to 4, preferably 2, in particular 1.

The ether splitting is carried out e.g. by boiling with hydriodic acid or hydrobromic acid or mixtures of hydrogen bromide/glacial acetic acid or by reaction with boron tribromide in inert solvents, such as chloroform, dichloromethane, at temperatures of −20 to 20°C.

The etherification is effected for example by reaction with alkyl halides in the presence of equivalent amounts of alkali metal alcoholate, e.g. sodium ethylate.

The debenzylation is effected by hydrogenolysis in the presence of catalysts, preferably palladium on charcoal, in solvents, such as methanol, ethanol, benzene, cyclohexane, at 0 to 50°, preferably room temperature, and a hydrogen pressure of 1—300 atmospheres, preferably 1—5 atmospheres.

The N-alkylation is carried out according to methods known to one skilled in the art. With suitable choice of the reaction conditions, the reaction is so conducted that either the N-alkyl derivatives are obtained, with alkyl including also the meaning of cycloalkyl, aralkyl and cycloalkylalkyl, or the alkylpyrrolidinium compounds are obtained. If the N-alkylation is so to be conducted that the N-alkyl derivatives are obtained, the N-alkylation is carried out with alkylating agents, such as alkyl halides, alkyl sulphonates, e.g. tosylates, alkyl sulphates, in inert solvents, such as acetone, methyl ethyl ketone; alcohols, such as methanol, ethanol, isopropanol, or without solvents, with the use of an auxiliary base, such as sodium carbonate, potassium carbonate, triethylamine, at temperatures of 20—100°C. If the N-alkylation is to be effected as N-quaternisation, i.e. with obtainment of the alkylpyrrolidinium compounds, the reaction is carried out in solvents, such as acetone, methyl ethyl ketone, ethyl acetate, alcohols, with alkylating agents, such as alkyl halides, alkyl tosylates, alkyl sulphates, at 20—100°C.

A, where appropriate, subsequent acylation of the free hydroxyl groups or amino groups is carried out according to methods known to the skilled man, e.g. by reaction with the appropriate acid anhydrides or halides (cf., inter alia, Houben-Weyl, Vol. 8, p. 543 ff. and 655 ff.). The splitting off of the acyl groups with liberation of the hydroxyl groups or amino groups is effected in the usual manner by hydrolysis, e.g. by reaction with suitable bases, such as sodium hydroxide solution or potassium hydroxide solution.

Acid addition salts are obtained by dissolving the free base in a suitable solvent, e.g. acetone, water, a low-molecular-weight aliphatic alcohol (ethanol, isopropanol) which contains the desired acid or to which the desired acid is subsequently added. The salts are obtained by filtration, precipitation with a non-solvent for the addition salt or by evaporation of the solvent.

The salts obtained, e.g. the hydrochlorides, can be converted into the free base

by neutralisation with aqueous sodium hydroxide or potassium hydroxide; the free base is then obtained by solvent extraction with a suitable water-immiscible solvent such as chloroform, dichloromethane, ether, benzene, toluene, cyclohexane. The free bases can also be obtained by neutralisation of an acid addition salt with sodium methylate in methanol and isolation of the base according to known processes. The salts can also be converted into the free bases by ion exchange. For this purpose, basic anion exchange resins, e.g. "Amberlite"[R] IRA 400 are used.

The racemate splitting is carried out in the usual manner, e.g. by addition of an optically active acid, such as mandelic acid, tartaric acid, camphor-sulphonic acid, dibenzoyltartaric acid, recrystallisation of the resultant salt until constancy of the specific rotation and liberation of the optically active base with solutions of alkali. From the mother liquors obtained during recrystallisation, there is obtained analogously the other enantiomer.

The reduction of the N-acyl-2-benzylpyrrolidines of the general formula IV is effected according to methods which are known per se, e.g. by reaction with a complex metal hydride as reducing agent in an anhydrous organic solvent and hydrolytic working up. Suitable reducing agents are, inter alia, lithium aluminium hydride and sodium dihydro - bis - (2 - methoxyethoxy) - aluminate or mixtures thereof. Suitable as solvents are inert anhydrous ethers, such as diethyl ether, tetrahydrofuran, dioxan, 1,2-dimethoxyethane and diethyleneglycol diethyl ether, and aromatic hydrocarbons, such as benzene and toluene, or mixtures of the said compounds. The temperature of the reaction is not critical and may vary within wide limits, for example from 0 to 100°C. Usually it is most expedient to carry out the reaction at the reflux temperature of the reaction mixture. The reaction duration is dependent on the reaction temperature used and may vary between 1 hour and 24 hours. In the case of the preferred reflux temperature, the reaction is normally ended in 3 to 4 hours. The reactants may be used in equivalent amounts, but an excess of the reducing agent is preferred. Following the reaction with the reducing agent, the reaction product is worked up by treatment of the reaction mixture with an aqueous medium, such as water, dilute aqueous inorganic acids or bases or other aqueous media. The product can be isolated as free base or as acid addition salt by adjustment of the pH value.

The preparation of the starting compounds of the formula III can be effected in accordance with the publications referred to in the state of the art. They are alternatively obtained by reaction of 1 - phenyl - 2,5 - dibromopentane with corresponding amines $R^1—NH_2$ in analogy to the process described by F. F. Blicke and B. A. Brown [J. Org. Chem. 26 (1961) 3685, particularly 3686 and 3689]. 2-Benzyl-pyrrolidine is also obtained by reduction of 2 - benzyl - 1 - nitroso - pyrrolidine.

The preparation of the starting compounds of the formula IV is likewise effected according to methods known to one skilled in the art, for example by acylation of the appropriate benzylpyrrolidines with carboxylic acid halides, such as Cl—CO—R^9, wherein R^9 has the meaning stated above, or carboxylic acid anhydrides in inert solvents, such as benzene, toluene, cyclohexane, chloroform, dichloromethane in the presence of an auxiliary base, such as pyridine, triethylamine, at temperatures between 0 to 50°C. Suitable carboxylic acid halides are for example acetyl chloride, propionyl chloride, butyryl chloride, pivaloyl chloride, cyclopropylcarbonyl chloride, cyclobutylcarbonyl chloride, benzoyl chloride, phenylacetyl chloride.

The following Examples explain the invention more fully, without restricting it. The abbreviation m.p. denotes melting point, b.p. denotes boiling point, decomp. denotes decomposition. Temperatures are stated in °C.

Example 1

2 - (4 - chlorobenzylidene) - 1 - methylpyrrolidine

a) From 9.66 g of p-chlorobenzyl chloride and 1.46 g of magnesium filings a Grignard solution in 100 ml of diethyl ether is prepared. To this is added dropwise, with stirring, a solution of 8.65 g of 2,2 - diethoxy - 1 - methylpyrrolidine in 50 ml of diethyl ether; the reaction mixture remains boiling. The mixture is kept at the boil for a further 1 hour, 10 ml of saturated ammonium chloride solution are added dropwise and the ether solution is collected. The residue is extracted three times with, in each case, 100 ml of ether, the united ether solutions are dried over magnesium sulphate and concentrated. After addition of 5 ml of methanol, the oily residue crystallises. 2.9 g (28% of theory) of m.p. 63° are obtained.

b) According to the method described in Example 22b), from 15 g of 2 - [α -

(cyano) - 4 - chlorobenzylidene] - 1 - methylpyrrolidine there are obtained 8.8 g (77%) of crystals, having a tendency to decompose, of m.p. 60—63°.

Example 2

2 - (4 - chlorobenzyl) - 1 - methylpyrrolidine

a) 28 g of 2 - p - chlorobenzylidene - 1 - methylpyrrolidine are dissolved in 250 ml of methanol and hydrogenated with Raney nickel as catalyst. Filtration from the catalyst is effected and the filtrate is concentrated. 22.7 g of the boiling point 75° at 0.005 mm Hg (yield: 81% of theory) are obtained. Recrystallised from ethanol, the picrate of the base melts at 149°.

By reaction of the base with the equivalent amount of the appropriate acid, the following salts are obtained:

hibenzate:	colourless viscous oil
citrate:	colourless oil
fumarate:	yellowish oil
benzoate:	yellow viscous oil
maleate:	light-yellow oil
oxalate:	pink oil
embonate:	yellow viscous oil

b) 40 g of 2 - [(α - ethoxycarbonyl) - 4 - chlorobenzylidene] - 1 - methylpyrrolidine and 150 ml of concentrated hydrochloric acid are boiled under reflux under the cessation of evolution of carbon dioxide. The cooled reaction mixture is rendered alkaline with 10% strength solution of sodium hydroxide and extraction is effected with 5×70 ml ether. After drying over sodium sulphate, the ether extract is concentrated and the solid residue is hydrogenated in 550 ml of ethanol with Pt/hydrogen. 27.6 g of the boiling point 75° at 0.005 mm Hg are obtained.

Example 3

2 - dimethylamino - 1 - methyl - 1 - pyrrolinium - methylsulphate

To a solution of 6.76 g of dimethylamine in 45 ml of benzene there are added dropwise, with stirring, 22.5 g of 2 - methoxy - 1 - methyl - 1 - pyrrolinium - methylsulphate and boiling under reflux is subsequently effected for 1 hour. The heavy phase is separated off, extracted twice by shaking out with diethyl ether and freed from solvent residues in a vacuum. 19.4 g (81.4% of theory) of reddish brown oil are obtained.

Example 4

2 - [1' - (ethoxycarbonyl) - 4 - chlorobenzylidene] - 1 - methylpyrrolidine

To a mixture of 99 g of 2 - dimethylamino - 1 - methyl - 1 - pyrrolinium - methylsulphate and 65 g of 4-chlorophenylacetic acid ethyl ester there is added dropwise, with stirring, at 100° bath temperature, in a stream of nitrogen, a solution of 9.6 g of sodium in 200 ml of ethanol. In doing so the alcohol is removed from the reaction mixture. Stirring is continued for a further 30 minutes at 100°; 200 ml of water are added to the cooled reaction mixture and extraction is effected with 5×100 ml of ether. The united ether extracts, after drying over sodium sulphate, are concentrated and a little excess 4-chlorophenylacetic acid ethyl ester is removed by heating in a high vacuum. Crude yield 86 g (94% of theory) of m.p. 71°.

Example 5

1 - isopropyl - 2 - methoxy - 1 - pyrrolinium - methylsulphate

89.6 g of 1-isopropylpyrrolidinone-2 and 88.9 g of dimethylsulphate are stirred for 3 hours at 80°. The reaction mixture is extracted 5 times with, in each case, 50 ml of ether and the red oil is dried in a high vacuum. 167.2 g (94% of theory) are obtained.

Thin-layer chromatography: layer silica gel neutral flow agent eluent chloroform/methanol 9:1, R_F value 0.30 colour detecting reagent: iodine vapour.

Example 6

1 - isopropyl - 2 - dimethylamino - 1 - pyrrolinium - methylsulphate

161 g of 1 - isopropyl - 2 - methoxy - 1 - pyrrolinium - methylsulphate are added dropwise, with stirring, to a solution of 43.8 g of dimethylamine in 283 ml of benzene. Subsequently, boiling under reflux is effected for 1.5 hours; the heavy

phase is separated off and washed 4 times with, in each case, 50 ml of diethyl ether. After drying in a high vacuum, 154 g (91% of theory) of reddish oil are obtained.

Example 7

2 - [1' - ethoxycarbonyl) - 4 - chlorobenzylidene] - 1 - isopropylpyrrolidine

To a mixture of 32 g of 4-chlorophenylacetic acid ethyl ester and 59.13 g of 1 - isopropyl - 2 - dimethylamino - 1 - pyrrolinium - methylsulphate there is added dropwise, with stirring, at 90—100°, in a stream of nitrogen, a solution of 5.1 g of sodium in 100 ml of ethanol. After completion of the addition, stirring is continued for a further 30 minutes, followed by cooling and taking up with water (~100 ml) and ether (~150 ml). The organic phase is collected, extraction is effected once again with ether, the united ether extracts are dried and concentration is effected. Crude yield 45.6 g (92% of theory); 5 g are recrystallised from ethanol/water. 4.2 g of m.p. 70—71° are obtained.

Example 8

2 - (4 - chlorobenzyl) - 1 - isopropylpyrrolidine

40.6 g of 2 - [(1 - ethoxycarbonyl) - 4 - chlorobenzylidene] - 1 - isopropylpyrrolidine and 115 ml of concentrated hydrochloric acid are boiled under reflux until the cessation of evolution of carbon dioxide. Alkalisation is effected with 250 ml of 6N sodium hydroxide solution, followed by extraction with 400 ml of ether, drying over sodium sulphate and concentration. The residue is dissolved in 250 ml of ethanol and hydrogenated with platinum/hydrogen. After the catalyst has been filtered off and the solvent has been distilled off, the product is distilled in a high vacuum. Yield 21.8 g (70% of theory) of b.p. 75° at 7.10^{-3}mm Hg.

A sample was converted into the picrate. m.p. 126—127° (from ethanol).

Example 9

2 - (4 - chlorobenzyl) - pyrroline - 1

a) To a Grignard solution, prepared from 22.3 g of magnesium filings and 147 g of 4-chlorobenzyl chloride in 250 ml of diethyl ether, there is added dropwise, with stirring, a solution of 83 g of 4-chlorobutyronitrile in 300 ml of ether. The mixture is kept at the boil for 1 hour, then the ether is distilled off and, simultaneously, 700 ml of xylene are added dropwise. Boiling under reflux (bath temp. 170°) is effected for 1 hour, followed by allowing to cool and adding slowly, with stirring, 150 ml of saturated ammonium chloride solution. The magnesium salts are filtered off and washed well with xylene and ether. The basic phases are extracted from the united organic components with 15% strength hydrochloric acid (250+150 ml), the aqueous phase is washed with 100 ml of ether and alkalisation is effected with 6N sodium hydroxide solution, with ice cooling. The separated oil is extracted with ether and, after drying over sodium sulphate, distilled. 22.3 g (16% of theory) of b.p. 109—113° at 0.01 mm Hg are obtained. The free base is unstable and is analysed as perchlorate.

m.p. of the perchlorate (from ethanol): 196—198°.

m.p. of the hydrochloride (from methanol/diethyl ether): 176—178°.

b) 80 g of 2 - (α - cyano - 4 - chlorobenzylidene) - pyrrolidine and 200 ml of concentrated hydrochloric acid are boiled under reflux for 2.5 hours; after cooling, alkalisation is effected with 3N sodium hydroxide solution, followed by extraction 3 times with, in each case, 200 ml of ether and, after drying over sodium sulphate, concentration to give a yellowish oil which is distilled in a vacuum. Yield 53.0 g (74%), b.p. 88—90° at 0.004 mm Hg.

Example 10

2 - (4 - chlorobenzyl) - pyrrolidine

28.5 g of 2 - (4 - chlorobenzyl) - pyrroline - 1 are hydrogenated in 300 ml of ethanol with Raney nickel/hydrogen. After removal of solvent and catalyst, distillation is effected in a high vacuum. 23.0 g (80% of theory) of b.p. 70—72° at 0.001 mm Hg are obtained.

m.p. of the hydrochloride (from methanol/diethyl ether): 190—192°.

Example 11

2 - methyl - (phenyl)amino - 1 - methyl - 1 - pyrrolinium - perchlorate

To 19.8 g of 1-methylpyrrolidinone-2 there are added dropwise 21.5 g of phosphorus oxytrichloride in such a manner that the temperature does not rise

above 40°. After 15 minutes, 16.5 g of N-methylaniline are added dropwise at 60°; 20 ml of 2N hydrochloric acid and 450 ml of ice water are added. To this solution are added 21.6 g of sodium perchlorate; colourless crystals are precipitated. 38.6 g (95% of theory) of product are obtained, which is recrystallised from isopropanol. m.p. 96.5—97°.

Example 12

2 - [(1' - methoxycarbonyl) - 3,4 - dimethoxybenzylidene] - 1 - methylpyrrolidine

To a mixture of 5.8 g of 2 - methyl - (phenyl) - amino - 1 - methyl - 1 - pyrrolinium - 1 - perchlorate and 4.5 g of homoveratric acid ethyl ester in 15 ml of pyridine there is added dropwise a solution of 0.46 g of sodium in 5 ml of methanol. Stirring is effected for 2 hours at 60°; pyridine and alcohol are distilled off in a vacuum and the oily residue is extracted with water and subsequently with petroleum ether. The mixture is put on to a silica gel column and chromatography is effected with chloroform/methanol 19:1. The eluate with an R_F value 0.76 is concentrated to give an oil. Yield 10.5% of theory.

Example 13

2 - [(1' - ethoxycarbonyl) - 3,4 - dimethoxybenzylidene] - 1 - methylpyrrolidine

To a mixture of 5.8 g of 2 - methyl - (phenyl) - amino - 1 - methyl - 1 - pyrrolinium - perchlorate and 4.5 g of homoveratric acid ethyl ester in 20 ml of ethanol there is added dropwise at room temperature with stirring a solution of 0.46 g of sodium in 10 ml of ethanol. Boiling under reflux is effected for 2 hours; alcohol and methylaniline are removed in a high vacuum and the residue is purified by column chromatography on silica gel. The product with the R_F value 0.72 in the flow agent chloroform/methanol 19:1 is collected. Yield 0.9 g (15% of theory).

Example 14

2 - (3,4 - dimethoxybenzylidene) - 1 - methylpyrrolidine

12.4 g of 2 - [(1 - methoxycarbonyl) - 3,4 - dimethoxybenzylidene] - 1 - methylpyrrolidine are boiled for 15 minutes with 40 ml of concentrated hydrochloric acid. After cooling, the mixture is rendered alkaline with sodium hydroxide solution; the precipitate is filtered off and recrystallised from ethanol/water 2:1. 3.2 g (32% of theory) of m.p. 72°.

Example 15

2 - (3,4 - dimethoxybenzyl) - 1 - methylpyrrolidine

12.2 g of 3,4 - dimethoxybenzylidene - 1 - methylpyrrolidine are dissolved in methanol and reduced with Raney nickel/hydrogen. After the catalyst has been filtered off and the methanol has been distilled off, the residue is distilled. 9.6 g (79%) of b.p. 90° at 0.005 mm Hg are obtained.

m.p. of the picrate (from ethanol) 105—106°.

Example 16

2 - (tert. - butoxycarbonyl - 4 - methoxyphenyl) - methylmercaptopyrroline - 1

18.4 g of thiopyrrolidinone-2 and 56 g of α - bromo - 4 - methoxyphenylacetic acid tert.-butyl ester are boiled for 3 hours in 300 ml of dichloromethane. After cooling, the organic phase is washed with 100 ml of 25% potassium carbonate solution and saturated sodium chloride solution; drying is effected over sodium sulphate, followed by concentration to give a yellowish oil which is recrystallised from 500 ml of n-hexane with activated charcoal. Yield 52.2 g (90% of theory), colourless crystals of m.p. 66—67°.

Example 17

2 - [1' - (tert. - butoxycarbonyl) - 4 - methoxybenzylidene] - pyrrolidine

25 g of 2 - (tert. - butoxycarbonyl - 4 - methoxyphenyl) - methyl - mercaptopyrroline - 1 and 1.0 g of potassium tert.-butylate are stirred in 160 ml of phosphorus acid trimethyl ester and 24 ml of dimethylsulphoxide under nitrogen at 100°. After 65 hours, the solvents are removed in a vacuum, the residue is dissolved in 200 ml of ether and the ether phase is extracted in each case once with 100 ml of water, 1N hydrochloric acid, dilute sodium carbonate solution and saturated sodium chloride solution. After drying and concentration, the residue is recrystallised from n-hexane. Yield 13.2 g (59% of theory), m.p. 98—100°.

Example 18

2 - (4 - methoxybenzyl) - pyrrolidine

To 15 g of 2 - [1' - (tert. - butoxycarbonyl) - 4 - methoxybenzylidene] - pyrrolidine there are added, with ice cooling, 80 ml of trifluoroacetic acid and stirring is effected for 2 hours at room temperature. The acid is distilled off in a vacuum, the residue is dissolved in 250 ml of ether and washing is effected with almost saturated cold sodium carbonate solution (150 ml) and saturated sodium chloride solution. After drying over sodium sulphate and the ether has been distilled off, the residue is dissolved in 300 ml of ethanol and reduced with Raney nickel/hydrogen. The solution is concentrated to an oil which is distilled in a vacuum. Yield 7.5 g (76%) of b.p. 88—90° at 0.008 mm Hg.

The hydrochloride (from ethanol/ether) melts at 141—142°.

Example 19

α - bromo - 3,4 - dimethoxyphenylacetic acid tert. - butyl ester

58.2 g of homoveratric acid tert.-butyl ester and 43.3 g of N-bromosuccinimide are heated under reflux for 2 hours in 1.3 litres of carbon tetrachloride under irradiation with a 500-watt immersion lamp. After cooling, filtration from the succinimide is effected and the filtrate is concentrated, which is dissolved in 250 ml of ether and is extracted by shaking with water. The ether solution is freed from the solvent in a vacuum. 50 g (66% of theory) of non-distillable oil remain behind.

Example 20

2 - (tert. - butoxycarbonyl - 3,4 - dimethoxyphenyl) - methylmercaptopyrroline - 1

15 g of thiopyrrolidinone-2 and 49 g of α - bromo - 3,4 - dimethoxyphenylacetic acid tert.-butyl ester are boiled for 1 hour in 200 ml of dichloromethane under reflux, washed with ice-cold potassium carbonate solution and saturated sodium chloride solution and, after drying over sodium sulphate, concentrated to a non-distillable oil. Yield 47.2 g (90% of theory).

Example 21

2 - [1' - tert. - butoxycarbonyl) - 3,4 - dimethoxybenzylidene] - pyrrolidine

35 g of 2 - tert. - butoxycarbonyl - 3,4 - dimethoxyphenyl) - methylmercaptopyrroline - 1 and 1.8 g of potassium tert.-butylate are stirred in 160 ml of phosphorous acid trimethyl ester and 23 ml of dimethylsulphoxide for 24 hours at 100° under nitrogen. The solvents are distilled off in a high vacuum, the residue is taken up with 300 ml of ether and 100 ml of 1N hydrochloric acid and the organic phase is treated with 100 ml of dilute sodium carbonate solution and saturated sodium chloride solution. After drying over sodium sulphate and the ether has been distilled off, 29.5 g (93%) of a light-brown, non-distillable oil are obtained.

Example 22

2 - (3,4 - dimethoxybenzyl) - pyrroline - 1

a) 29.3 g of 2 - [1' - (tert. - butoxycarbonyl) - 3,4 - dimethoxybenzylidene] - pyrrolidine are dissolved in 120 ml of trifluoroacetic acid, with ice cooling, and stirred at room temperature for 2 hours. After the acid has been distilled off, the residue is dissolved in 500 ml of ether and extracted with cold saturated sodium carbonate solution and saturated sodium chloride solution. After drying over sodium sulphate and concentration, 14.6 g of yellowish oil remain behind (72% of theory).

The picrate (from ethanol) melts at 139—141°.

b) 24.4 g of 2 - [α - (cyano) - 3,4 - dimethoxybenzylidene] - pyrrolidine are boiled with 60 ml of concentrated hydrochloric acid under reflux for 15 minutes; after cooling, alkalisation is effected with 6N sodium hydroxide solution and the base is extracted with ether. After the solvent has been distilled off, 16.0 g (73%) of a yellowish oil remain behind.

Example 23

2 - (3,4 - dimethoxybenzyl) - pyrrolidine

a) 13.1 g of 2 - (3,4 - dimethoxybenzyl) - pyrroline - 1 are hydrogenated in 300 ml of ethanol with Raney nickel/hydrogen. Filtration from the catalyst is effected, the filtrate is concentrated, the residue is distilled and 3.6 g of b.p. 116° at 0.007 mm Hg are obtained. Further purification is effected by column

chromatography on silica gel. The product with R_F value 0.36 (flow agent eluent chloroform/methanol 4:1, carrier silica gel) is collected. Yield 504 mg (5% of theory).

A sample of the picrate (from ethanol) melts at 180—181°; a sample of the hydrogen fumarate (from ethanol) melts at 165—166°.

b) 11.7 g of 1 - benzyl - 2 - (3,4 - dimethoxybenzyl) - pyrrolidine are hydrogenated in ethanol with 6.5 g of palladium/activated charcoal (10% strength)/hydrogen. The product, freed from solvent and catalyst, is distilled in a high vacuum. After purification via the picrate, 3.2 g (38.5% of theory) are obtained.

Example 24

2 - dimethylamino - 1 - benzyl - 1 - pyrrolinium - 1 - methylsulphate

35 g of 1-benzylpyrrolidinone-2 and 25.2 g of dimethylsulphate are heated at 80° for 8 hours. The reaction mixture is extracted several times with ether and benzene, and the viscous oil is then added dropwise, with stirring, to a solution of 20 ml of dimethylamine in 80 ml of benzene. Boiling under reflux is effected for 1 hour, the heavy phase is collected and extraction is effected 3 times with ether.

Yield 35.4 g (55% of theory) of viscous oil.

Example 25

1 - benzyl - 2 - [1' - (ethoxycarbonyl) - 3,4 - dimethoxybenzylidene] - pyrrolidine

To 34.5 g of 2 - dimethylamino - 1 - benzyl - 1 - pyrrolinium - methylsulphate and 19.7 g of homoveratric acid ethyl ester there is added dropwise at 90°, with stirring, in a stream of nitrogen, a solution of 2.6 g of sodium in 50 ml of ethanol. The mixture is kept at this temperature for a further 30 minutes, the reaction mass is distributed between water and ether, the ether solution is dried over sodium sulphate and concentration is effected. Yield 32.2 g (96% of theory).

Example 26

1 - benzyl - 2 - (3,4 - dimethoxybenzylidene) - pyrrolidine

31.5 g of 1 - benzyl - 2 - [1' - (ethoxycarbonyl) - 3,4 - dimethoxybenzylidene] - pyrrolidine are boiled under reflux with 75 ml of concentrated hydrochloric acid until the cessation of evolution of carbon dioxide. After cooling, alkalisation is effected with sodium hydroxide solution and the precipitate formed is recrystallised from ethanol. Yield 11.3 g (44% of theory) of m.p. 105°.

Example 27

1 - benzyl - 2 - (3,4 - dimethoxybenzyl) - pyrrolidine

3 g of 1 - benzyl - 2 - (3,4 - dimethoxybenzylidene) - pyrrolidine are dissolved in ethanol and hydrogenated with platinum/hydrogen. Distillation in a vacuum gives 2.3 g (77%) of b.p. 173° at 0.007 mm Hg.

The picrate (from ethanol) melts at 153°.

Example 28

2 - [1' - (ethoxycarbonyl) - 4 - nitrobenzylidene] - 1 - methylpyrrolidine

50 g of 4-nitrophenylacetic acid ethyl ester and 41.4 g of 2,2 - diethoxy - 1 - methylpyrrolidine are boiled under reflux for 3 hours in 250 ml of benzene. After the benzene has been distilled off, the residue is recrystallised from ether/petroleum ether.

Yield 52.6 g (77% of theory) of red crystals of m.p. 82—83°.

Example 29

1 - methyl - 2 - (4 - nitrobenzylidene) - pyrrolidine

a) 11 g of 2 - [1' - (ethoxycarbonyl) - 4 - nitrobenzylidene] - 1 - methylpyrrolidine are boiled in 100 ml of concentrated hydrochloric acid until the cessation of evolution of carbon dioxide. Alkalisation is effected with sodium hydroxide solution; the red precipitate (8.7 g) is filtered off and a sample is recrystallised from ethanol. m.p. 133—134°.

b) To a mixture of 5.0 g of 2 - dimethylamino - 1 - methyl - 1 - pyrrolinium-methylsulphate and 2.2 g of 4-nitrotoluene in 15 ml of dimethylformamide there is added dropwise at 130° a solution of 2.35 g of potassium tert.-butanolate in 15 ml of tert.-butanol and 10 ml of dimethylformamide. Stirring is effected at this temperature for 2 hours; the mixture is allowed to cool, water is added and extraction is effected several times with

chloroform. The united chloroform extracts are concentrated; a slight excess of 4-nitrotoluene is distilled off in a high vacuum and the residue is recrystallised from 10 ml of ethanol. 0.8 g of the title compound is obtained.

Example 30

2 - (4 - aminobenzyl) - 1 - methylpyrrolidine

a) 8.5 g of 1 - methyl - 2 - (4 - nitrobenzylidene) - pyrrolidine are reduced in ethanol with platinum/hydrogen. After removal of catalyst and solvent, recrystallisation is effected from n-hexane. 3.6 g (49% of theory) of m.p. 59—61°.

m.p. of the hydrobromide (from ethanol/ether): 193—196°.

m.p. of the dihydrobromide (from ethanol/diethyl ether): 267—270°.

m.p. of the dihydrochloride (from ethanol/diethyl ether): 244° (decomp.).

b) 18 g of 2 - (4 - nitrobenzyl) - 1 - methylpyrrolidine are hydrogenated in ethanol with 300 mg of platinum dioxide/hydrogen. Filtration from the catalyst is effected, followed by concentration, and the residue is recrystallised from n-hexane. Yield 12.7 g (82% of theory).

Example 31

2 - [1' - (ethoxycarbonyl) - benzylidene] - 1 - methylpyrrolidine

To 84 g of 2 - dimethylamino - 1 - methyl - 1 - pyrrolinium - methylsulphate and 37.9 g of phenylacetic acid ethyl ester there is added dropwise at 90°, with stirring, in a stream of nitrogen, a solution of 6.9 g of sodium in 140 ml of ethanol. Stirring is effected for a further 30 minutes at 90°, the reaction mixture is distributed between water and ether (300 ml of each) and the product isolated from the ether phase is distilled. Yield 48 g (85% of theory) of b.p. 106—107° at 0.008 mm Hg.

Example 32

2 - [1' - (ethoxycarbonyl) - 2 - methoxybenzylidene] - 1 - methylpyrrolidine

According to the method of working described in Example 31, from 50 g of 2-methoxyphenylacetic acid ethyl ester, 83.4 g of 2 - dimethylamino - 1 - methyl - 1 - pyrrolinium - methylsulphate and a solution of 8.1 g of sodium in 160 ml of ethanol, there are obtained 63.8 g of 2 - [1' - (ethoxycarbonyl) - 2 - methoxybenzylidene] - 1 - methylpyrrolidine (71% of theory) of b.p. 134—137° at 0.005 mm Hg.

Example 33

2 - [1' - (ethoxycarbonyl) - 3,4,5 - trimethoxybenzylidene] - 1 - methylpyrrolidine

According to the method of working described in Example 31, from 51.7 g of 2 - dimethylamino - 1 - methyl - 1 - pyrrolinium-methylsulphate, 40.6 g of 3,4,5-trimethoxyphenylacetic acid ethyl ester and a solution of 5.0 g of sodium in 100 ml of ethanol, there are obtained 36.2 g of 2 - [1' - (ethoxycarbonyl) - 3,4,5 - trimethoxybenzylidene] - 1 - methylpyrrolidine of m.p. 115—116°, recrystallised from cyclohexane.

Example 34

2 - [1' - (ethoxycarbonyl) - 4 - methoxybenzylidene] - 1 - methylpyrrolidine

According to the method of working described in Example 31, from 4.8 g of 2 - dimethylamino - 1 - methyl - 1 - pyrrolinium - methylsulphate, 3.5 g of 4-methoxyphenylacetic acid ethyl ester and a solution of 0.46 g of sodium in 10 ml of ethanol, there is obtained 1 g (20% of theory) of 2 - [1' - (ethoxycarbonyl) - 4 - methoxybenzylidene] - 1 - methylpyrrolidine of m.p. 81—82°.

Example 35

2 - [1' - (ethoxycarbonyl) - 2 - chlorobenzylidene] - 1 - methylpyrrolidine

According to the method of working described in Example 31, from 98.4 g of 2 - dimethylamino - 1 - methyl - 1 - pyrrolinium - methylsulphate, 56.1 g of 2-chlorophenylacetic acid ethyl ester and a solution of 9.5 g of sodium in 190 ml of ethanol, there are obtained 73.8 g (93% of theory) of 2 - [1' - (ethoxycarbonyl) - 2 - chlorobenzylidene] - 1 - methylpyrrolidine of b.p. 129° at 0.008 mm Hg.

Example 36

2 - [1' - (ethoxycarbonyl) - 3 - chlorobenzylidene] - 1 - methylpyrrolidine

According to the method of working described in Example 31, from 91 g of 2 - dimethylamino - 1 - methyl - 1 - pyrrolinium - methylsulphate, 55.1 g of 3-

chlorophenylacetic acid ethyl ester and a solution of 8.8 g of sodium in 175 ml of ethanol, there are obtained 70 g (90% of theory) of 2 - [1' - (ethoxycarbonyl) - 3 - chlorobenzylidene] - 1 - methylpyrrolidine of b.p. 137° at 0.006 mm Hg.

Example 37

2 - [1' - (ethoxycarbonyl) - 4 - bromobenzylidene] - 1 - methylpyrrolidine

According to the method of working described in Example 31, from 54.3 g of 4-bromophenylacetic acid ethyl ester, 74.3 g of 2 - dimethylamino - 1 - methyl - 1 - pyrrolinium - methylsulphate and a solution of 7.2 g of sodium in 145 ml of ethanol, there are obtained 62.4 g (87% of theory) of 2 - [1' - (ethoxycarbonyl) - 4 - bromobenzylidene] - 1 - methylpyrrolidine of b.p. 128° at 0.006 mm Hg.

Example 38

2 - [1' - (ethoxycarbonyl) - 4 - fluorobenzylidene] - 1 - methylpyrrolidine

According to the method of working described in Example 31, from 4.8 g of 2 - dimethylamino - 1 - methyl - 1 - pyrrolinium - methylsulphate, 3.3 g of 4-fluorophenylacetic acid ethyl ester and a solution of 0.46 g of sodium in 10 ml of ethanol, there are obtained 1.7 g (36% of theory) of 2 - [1' - (ethoxycarbonyl) - 4 - fluorobenzylidene] - 1 - methylpyrrolidine of m.p. 80°, purified by column chromatography on silica gel.

Example 39

2 - benzyl - 1 - methylpyrrolidine

According to the method of working described in Example 2b), from 20 g of 2 - [1' - (ethoxycarbonyl) - benzylidene] - 1 - methylpyrrolidine, there are obtained 10.7 g of 2 - benzyl - 1 - methylpyrrolidine of b.p. 44—48° of 0.005 mm Hg.

Example 40

2 - (3 - chlorobenzyl) - 1 - methylpyrrolidine

According to the method of working described in Example 2b), from 62.5 g of 2 - [1' - (ethoxycarbonyl) - 3 - chlorobenzylidene] - 1 - methylpyrrolidine, there are obtained 34 g (72% of theory) of 2 - (3 - chlorobenzyl) - 1 - methylpyrrolidine of b.p. 81° at 0.007 mm Hg. m.p. of the picrate (from ethanol) 186°.

Example 41

2 - (2 - chlorobenzyl) - 1 - methylpyrrolidine

According to the method of working described in Example 2b), from 61 g of 2 - [1' - (ethoxycarbonyl) - 2 - chlorobenzylidene] - 1 - methylpyrrolidine, there are obtained 35.6 g (78% of theory) of 2 - (2 - chlorobenzyl) - 1 - methylpyrrolidine of b.p. 81° at 0.008 mm Hg.

The picrate (from ethanol) melts at 170°.

Example 42

2 - (4 - bromobenzylidene) - 1 - methylpyrrolidine

According to the method of working described in Example 14, from 59.9 g of 2 - [1' - (ethoxycarbonyl) - 4 - bromobenzylidene] - 1 - methylpyrrolidine there are obtained 28.3 g of 2 - (4 - bromobenzylidene) - 1 - methylpyrrolidine of m.p. 83—84° (recrystallised from ethanol).

Example 43

2 - (4 - bromobenzyl) - 1 - methylpyrrolidine

21.5 g of 2 - (4 - bromobenzylidene) - 1 - methylpyrrolidine are hydrogenated in 400 ml of ethanol with platinum on activated charcoal/hydrogen. Filtration from the catalyst is effected, followed by concentration, and the residue is distilled. 18.5 g (85% of theory) of b.p. 70° at 0.001 mm Hg are obtained.

The picrate (from ethanol) melts at 140—142°.

Example 44

2 - (4 - fluorobenzyl) - 1 - methylpyrrolidine

According to the method of working described in Example 2b) (hydrogenation catalyst=platinum), from 20 g of 2 - [(1' - ethoxycarbonyl) - 4 - fluorobenzylidene] - 1 - methylpyrrolidine there are obtained 7.5 g of 2 - (4 - fluorobenzyl) - 1 - methylpyrrolidine of b.p. 57° at 0.006 mm Hg.

The picrate (from ethanol) melts at 168°.

Example 45

2 - (2 - methoxybenzyl) - 1 - methylpyrrolidine

According to the method of working described in Example 2b), from 55 g of 2 - [1' - (ethoxycarbonyl) - 2 - methoxybenzylidene] - 1 - methylpyrrolidine there are obtained 22.3 g (54%) of b.p. 73° at 0.005 mm Hg.

The picrate (from ethanol) melts at 144° .

Example 46

2 - (4 - methoxybenzyl) - 1 - methylpyrrolidine

a) According to the method of working described in Example 2b), from 11 g of 2 - [1' - (ethoxycarbonyl) - 4 - methoxybenzylidene] - 1 - methylpyrrolidine (hydrogenation catalyst=platinum; purification by column chromatography on silica gel) there are obtained 7 g (85% of theory) of the title compound.

The picrate (from ethanol) melts at 139°.

b) 0.8 g of 2 - [1' - (cyano) - 4 - methoxybenzylidene] - 1 - methylpyrrolidine is heated under reflux for 15 minutes in 12 ml of concentrated hydrochloric acid. 30 ml of ice water are added, alkalisation is effected with 6 N sodium hydroxide solution, and the base is extracted with ether. After the solvent has been distilled off, the oily residue (440 mg) is dissolved in ethanol and hydrogenated with platinum/hydrogen. After freeing from the catalyst and the solvent has been distilled off, 320 mg (45%) of a yellowish liquid of b.p. 79° at 0.005 mm Hg are obtained.

Example 47

1 - methyl - 2 - (3,4,5 - trimethoxybenzyl) - pyrrolidine

According to the method of working described in Example 2b), from 30.2 g of 2 - [1' - (ethoxycarbonyl) - 3,4,5 - trimethoxybenzylidene] - 1 - methylpyrrolidine there are obtained 15.2 g of 1 - methyl - 3,4,5 - trimethoxybenzylpyrrolidine of b.p. 118° at 0.006 mm Hg.

(Hydrogenation catalyst:platinum).

The picrate (from ethanol) melts at 125°.

Example 48

2 - (3 - methoxybenzyl) - 1 - methylpyrrolidine

To 83.4 g of 2 - dimethylamino - 1 - methyl - 1 - pyrrolinium - methylsulphate and 48.3 g of 3-methoxyphenylacetic acid ethyl ester there is added dropwise at 90°, with stirring, in a stream of nitrogen, a solution of 8.1 g of sodium in 160 ml of ethanol. Stirring is effected for a further 30 minutes at 90°, the reaction mixture is distributed between 300 ml of water and 300 ml of ether, the ether phase is concentrated and the residue is boiled with concentrated hydrochloric acid until the cessation of evolution of carbon dioxide. After cooling, alkalisation is effected with 6N sodium hydroxide solution, followed by extraction with ether; the ether extract is dried over sodium sulphate, concentrated, and reduced in methanol with platinum/hydrogen. Filtration from the catalyst is effected, followed by concentration and distillation. Yield 23.0 g (45% of theory) of b.p. 88° at 0.005 mm Hg.

The picrate (from ethanol) melts at 166°.

Example 49

2 - (4 - nitrobenzyl) - 1 - methylpyrrolidine

27.9 g of 2 - benzyl - 1 - methylpyrrolidine are dissolved in 130 ml of concentrated sulphuric acid, and 100 ml of concentrated nitric acid are added dropwise at 0°, with stirring. Stirring is effected for a further 30 minutes at room temperature; the mixture is poured into 1 litre of ice water and alkalised with sodium hydroxide solution, with cooling. Extraction is effected 4 times with, in each case, 150 ml of ether, the ether phase is dried over sodium sulphate and concentration to a red oil is effected. Yield 33.8 g (96% of theory). The hydrogen fumarate (from isopropanol) melts at 145—146°.

Example 50

2 - (3 - hydroxybenzyl) - 1 - methylpyrrolidine

10.5 g of 2 - (3 - methoxybenzyl) - 1 - methylpyrrolidine are boiled under reflux for 50 hours in a mixture of 60 ml of acetic acid and 60 ml of 48% strength hydrobromic acid. The mixture is poured on to ice, neutralized to pH 10 with 6N sodium hydroxide solution and extracted 3 times with ether. After drying of the united ether phase, the solvent is distilled off and the residue is distilled in a

vacuum. Yield 7.95 g (79% of theory) of b.p. 128—130° at 0.006 mm Hg. The fumarate (from isopropanol) melts at 189—191°.

Example 51

2 - (4 - hydroxybenzyl) - 1 - methylpyrrolidine

6.2 g of 2 - (4 - methoxybenzyl) - 1 - methylpyrrolidine are boiled under reflux for 24 hours in a mixture of 30 ml of acetic acid and 30 ml of 48% strength hydrobromic acid; a further 20 ml of acetic acid and 20 ml of hydrobromic acid are added and boiling is continued for a further 24 hours. The mixture is poured on to 400 ml of ice water, neutralised to pH 10 with 6N sodium hydroxide solution and extracted 4 times with, in each case, 50 ml of ether. After drying over sodium sulphate and the solvent has been distilled off, the residue is recrystallised from 25 ml of ethanol. Yield 65% of theory. m.p. 161—162°.

Example 52

2 - (3,4 - dihydroxybenzyl) - 1 - methylpyrrolidine

5.0 g of 2 - (3,4 - dimethoxybenzyl) - 1 - methylpyrrolidine are boiled under reflux reflux for 41 hours in a mixture of 45 ml of acetic acid and 45 ml of 48% strength hydrobromic acid. The bulk of the acid is removed through distillation in a vacuum, the residue is taken up with ice water and alkalisation is effected with sodium carbonate solution. After several hours' extraction of the base with ether, the residue (4.1 g) obtained after the solvent has been distilled off is converted into the hydrochloride with methanol/ethereal hydrochloric acid. Yield 3.4 g (67% of theory). m.p. 188°.

Example 53

2 - [1′ - (cyano) - 4 - chlorobenzylidene] - 1 - methylpyrrolidine

22.7 g of 2,2 - diethoxy - 1 - methylpyrrolidine, 19.8 g of 4-chlorobenzylcyanide and 90 ml of benzene are boiled for 1 hour under reflux and with stirring. The volatile constituents are distilled off in a vacuum; the residue, after trituration with a little ether, is filtered off. Yield 20.8 g (68% of theory), m.p. 71—72° (from isopropanol).

According to the method of working described in Example 60, from 36 g of 2 - methoxy - 1 - methylpyrrolinium - 1 - methylsulphate, 24 g of p-chlorobenzylcyanide and a solution of 6.1 g of sodium in 100 ml of ethanol there are obtained 23 g of the title compound, yield 53%, m.p. 70—72°.

Example 54

2 - [1′ - (cyano) - 4 - methoxybenzylidene] - 1 - methylpyrrolidine

30.0 g of 2,2 - diethoxy - 1 - methylpyrrolidine, 25 g of 4-methoxybenzylcyanide and 150 ml of benzene are boiled under reflux for 4 hours. Concentration is effected and the residue is distilled twice in a vacuum. Yield 30.6 g (79% of theory), b.p. 158° at 0.005 mm Hg.

Example 55

2 - (3 - methylbenzyl) - 1 - methylpyrrolidine

From 103 g of 3-methylbenzyl chloride and 18 g of magnesium in 400 ml of ether a Grignard solution is prepared. To this is added dropwise, with stirring and boiling under reflux, a solution of 126.9 g of 2,2 - diethoxy - 1 - methylpyrrolidine. The mixture is kept at the boil for a further 1 hour, 130 ml of saturated ammonium chloride solution are added dropwise, the magnesium salts are filtered off and drying is effected over sodium sulphate. The residue (31 g) free from ether is hydrogenated with Raney nickel/hydrogen and distilled twice in a vacuum. Yield 16.2 g (13% of theory), b.p. 56° at 0.001 mm Hg.

The picrate (from ethanol) melts at 135—137°.

Example 56

2 - (4 - bromobenzyl) - 1 - methylpyrrolidine

To 2 g of 2 - benzyl - 1 - methylpyrrolidine and 50 mg of iron powder there are added 11.4 mmoles of bromine at room temperature. The mixture is left to stand for 2 hours, rendered alkaline with 1 N sodium hydroxide solution, and the base is extracted with ether; distillation is effected and 2 - (4 - bromobenzyl) - 1 - methylpyrrolidine is obtained as almost colourless liquid of b.p. 72° at 0.001 mm Hg.

Example 57

2 - (4 - chlorobenzyl) - pyrrolidine

20 g of 2 - (4 - chlorobenzoyl) - pyrrole, 15 g of hydrazine hydrate, 28 g of potassium hydroxide and 100 ml of diethylene glycol are heated to 150° for 2 hours. The mixture is allowed to cool, diluted with water to twice the volume, hydrochloric acid is added until there is a pH of 3, extraction is effected with ether, the organic phase is freed from solvent, the oil [2 - (4 - chlorobenzyl) - pyrrole] remaining behind is dissolved in 25 ml of ethanol and this solution, boiling hot, is added dropwise to a mixture of 150 ml of 20% strength hydrochloric acid and zinc amalgam (prepared from 100 g of zinc, 10 g of mercury chloride and 150 ml of 0.5N hydrochloric acid). A further 200 ml of 20% strength hydrochloric acid and 50 g of amalgam are then added and boiling is effected for a further 4 hours; the mixture is allowed to cool, filtered, extracted with ethyl acetate (5×200 ml), the organic solution is concentrated, 6N sodium hydroxide solution is added until the zinc salts have dissolved; and extraction is effected with ether. The ether solution is concentrated; the oil remaining behind is dissolved in 200 ml of alcohol and hydrogenated on Pt/C contact. Filtration from the catalyst is effected, followed by concentration and by distillation in a vacuum and 2 - (4 - chlorobenzyl) - pyrrolidine [b.p. 76—79° at 0.005 mm Hg] is obtained, the hydrochloride of which melts at 190—192°.

Example 58

2 - (4 - methoxybenzyl) - pyrrolidine

3.3 g of 2 - (p - methoxybenzyl) - pyrroline - 3 in 100 ml of ethanol are hydrogenated on Pt/C catalyst. The solution freed from the catalyst is concentrated and the oily residue is treated with ethanol/ethereal hydrochloric acid. 2 - (4 - methoxybenzyl) - pyrrolidine hydrochloride of m.p. 140—142° (ethanol/ether) is obtained.

Example 59

1 - tert. - butyl - 2 - methoxy - 1 - pyrrolinium - methylsulphate

108.8 g of 1 - tert. - butylpyrrolidinone - 2 and 97.0 g of dimethylsulphate are stirred at 80° for 3 hours. The mixture is allowed to cool to 35—40°, with stirring; absolute ether is added and the crystallised salt is filtered off. Yield 164.4 g (80%), m.p. 57—62°.

Example 60

1 - tert. - butyl - 2 - (α - cyano - 4 - chlorobenzylidene) - pyrrolidine

56.8 g of 1 - tert. - butyl - 2 - methoxy - 1 - pyrrolinium - methylsulphate and 30.3 g of 4-chlorobenzylcyanide are heated to 80°; a solution of 8.1 g of sodium in 160 ml of ethanol is added dropwise within 2 hours, with stirring; after completion of the addition, boiling is effected for a further 2 hours, followed by concentration, and the excess 4-chlorobenzylcyanide is distilled off at 10^{-3} mm Hg. The residue is recrystallised from 170 ml of ethanol. 11 g are obtained, and from the concentrated mother liquor a further 2.5 g (24%), of light-brown crystals of m.p. 150—153°.

Example 61

2 - [(1' - ethoxycarbonyl) - 4 - chlorobenzylidene] - 1 - methylpyrrolidine

According to the method of working described in Example 60, from 30 g of 4-chlorophenylacetic acid ethyl ester and 36.1 g of 2 - methoxy - 1 - methyl - 1 - pyrrolinium - methylsulphate there are obtained 20.1 g (77%) of the title compound, b.p. 132—134° at 0.005 mm Hg. 9.1 g of 4-chlorophenylacetic acid ester are recovered.

Example 62

2 - (α - cyano - 4 - chlorobenzylidene) - pyrrolidine

106 g of 2-methoxypyrroline-1, 243.5 g of 4-chlorobenzylcyanide and 9 ml of triethylamine are stirred for 20 hours at 110°; after cooling, 200 ml of ether are added and the precipitate (80.9 g) is filtered off. From the filtrate there are obtained, after the solvent and the 4-chlorobenzylcyanide have been distilled off in a vacuum, a further 42 g. Total yield 122.9 g (52%), m.p. 135—137°.

Example 63

2 - [(4 - biphenylyl) - cyanomethylene] - pyrrolidine

32.7 g of 2-methoxypyrroline, 63.8 g of 4-phenylbenzylcyanide and 5 g of 1,5 - diazabicyclo[5,4,0] - undec - 5 - ene are stirred for 26 hours at 110°; after cooling, the mixture is taken up with 500 ml of ether, the precipitate is filtered and

recrystallised from 400 ml of ethanol with activated charcoal. Yield 12.2 g (14%), m.p. 168—170°.

Example 64

1 - methyl - 2 - (3,4,5 - trihydroxybenzyl) - pyrrolidine

3.6 of 1 - methyl - 2 - (3,4,5 - trimethoxybenzyl) - pyrrolidine, 30 ml of 48% strength hydrobromic acid and 30 ml of acetic acid are boiled under reflux for 9 hours; a further 10 ml of hydrobromic acid and 10 ml of acetic acid are added and boiling is continued for a further 3 hours. Subsequently, concentration to dryness is effected and the residue is recrystallised twice from methanol/ether. Yield 2.56 g (61%) of slightly pink crystals; m.p. of the hydrobromide 168—171°.

Example 65

2 - (4 - chlorobenzyl) - 1 - cyclopropylcarbonylpyrrolidine

To 10 g of 2 - (4 - chlorobenzyl) - pyrrolidine and 6.2 g of triethylamine there are added dropwise, at 0 to 8°, 5.2 g of cyclopropanecarboxylic acid chloride in 10 ml of dichloromethane. Stirring is effected for a further 2 hours at 0°; water is added, the organic phase is separated off, extraction is again effected with dichloromethane, the united organic phases are washed with dilute hydrochloric acid and sodium carbonate solution, drying over sodium sulphate is effected and the oily residue obtained after the solvent has been evaporated off is distilled. Yield 8.85 g of oil (b.p. 135—137° at 0.005 mm Hg), which solidifies to give a crystalline mass of m.p. 62—64°.

Example 66

2 - (4 - chlorobenzyl) - 1 - cyclopropylmethylpyrrolidine

3.0 g of 2 - (4 - chlorobenzyl) - 1 - cyclopropylcarbonylpyrrolidine, dissolved in 30 ml of tetrahydrofuran, are added dropwise within 10 minutes at 0°, with stirring, to a suspension of 0.43 g of lithium aluminium hydride (=lithium hydridoaluminate) in 10 ml of tetrahydrofuran. Subsequently, boiling under reflux is effected for 1 hour; after cooling, 50 ml of water are cautiously added and extraction is effected 3 times with, in each case, 30 ml of ether. The united ether solutions are washed with saturated sodium chloride solution; drying over sodium sulphate is effected and, after the solvent has been evaporated off, the residue is distilled twice in a vacuum. Yield 1.65 g (58%); b.p. 108° at 0.006 mm Hg.

Example 67

1 - allyl - 2 - (4 - chlorobenzyl) - pyrrolidine

5 g of 2 - (4 - chlorobenzyl) - pyrrolidine, 3.53 g of anhydrous potassium carbonate, 3.4 g of allyl bromide and 50 ml of ethyl methyl ketone are boiled under reflux for 1 hour; the solvent is evaporated off, the residue is taken up with 50 ml of water and extraction is effected 3 times with, in each case, 30 ml of ether. The united ether phases are dried over sodium sulphate, the solvent is distilled off and the residue is distilled in a vacuum. Yield 5.12 g (85%), b.p. 84—87° at 0.005 mm Hg. m.p. of the picrate (from ethanol) 115—117°.

Example 68

2 - (4 - chlorobenzyl) - 1 - hexylpyrrolidine

5 g of 2 - (4 - chlorobenzyl) - pyrrolidine, 3.53 g of anhydrous potassium carbonate, 4.6 g of 1-bromohexane and 50 ml of ethyl methyl ketone are boiled under reflux for 18 hours. Working up is effected as in Example 67 and 5.82 g (81%) of a colourless liquid of b.p. 110—112° at 0.005 mm Hg are obtained.

Example 69

2 - (3,4 - diacetoxybenzyl) - 1 - methylpyrrolidine

3.25 g of 2 - (3,4 - dihydroxybenzyl) - 1 - methylpyrrolidine are left to stand for 24 hours in 30 ml of acetic anhydride/pyridine 1:1. Concentration in a vacuum is effected and, after distillation of the residue, 3.5 g (76%) of a yellowish oil (b.p. 135—140° at 0.005 mm Hg) are obtained which, during standing, solidifies to give a crystalline mass of m.p. 44—45°.

Example 70

2 - (4 - chlorobenzyl) - 1,1 - dimethylpyrrolidinium iodide

To 5.5 g of 2 - (4 - chlorobenzyl) - 1 - methylpyrrolidine in 40 ml of acetone there are added dropwise, with stirring, 3.72 g of methyl iodide. The crystalline precipitate is filtered off and recrystallised twice from methanol/ether. Yield 6.9 g (75%), m.p. 184—186°.

Example 71

2 - [(1' - ethoxycarbonyl) - 2,4 - dichlorobenzylidene] - 1 - methylpyrrolidine

According to the method of working described in Example 4, from 47.7 g of 2-dimethylamino - 1 - methyl - 1 - pyrrolinium methylsulphate and 23 g of 2,4-dichlorophenylacetic acid ethyl ester there are obtained 19 g (61%) of a reddish oil of b.p. 130° at 0.001 mm Hg.

Example 72

2 - (2,4 - dichlorobenzyl) - 1 - methylpyrrolidine

According to the method of working described in Example 2b), from 18.5 g of 2 - [(1' - ethoxycarbonyl) - 2,4 - dichlorobenzylidene] - 1 - methylpyrrolidine there are obtained 10.4 g (72%) of a colourless liquid of b.p. 91° at 0.005 mm Hg. The picrate (from ethanol) melts at 174—176°.

Example 73

(+) - 2 - (4 - chlorobenzyl) - 1 - methylpyrrolidine

To 15 g of 2 - (4 - chlorobenzyl) - 1 - methylpyrrolidine, dissolved in 100 ml of acetone, there is added a solution of 27 g of dibenzoyl-L-tartaric acid in 200 ml of acetone. The mixture is allowed to stand for 6 hours at room temperature and for 4 days at 0°, the crystals (8.5 g) are filtered off, the filtrate is concentrated somewhat, the mixture is again left to stand for 12 hours at 0°, the latterly precipitated crystals (4.53 g) are collected, the collected crystalline products are recrystallised from 100 ml of acetone, and 9.9 g of dibenzoyl tartrate, m.p. 117—120°, $[\alpha]_{589}^{20}$=—64° (25 mg/ml in methanol) are obtained. 9.4 g of this salt are shaken with ether/sodium hydroxide solution until dissolving is complete; the ether phase is dried, the solvent is evaporated off and the residue is distilled. 2.73 g of the base of b.p. 70° at 0.005 mm Hg are obtained; $[\alpha]_{589}^{20}$=+78.9° (25 mg/ml in methanol).

From the united filtrates there is isolated the laevo-rotatory enantiomer with an optical purity of 0.158, $[\alpha]_{589}^{20}$=—12.5°.

Example 74

2 - (4 - biphenylylmethyl) - pyrrolidine

10 g of 2 - [(4 - biphenylyl) - cyanomethylene] - pyrrolidine are boiled for 30 minutes with 30 ml of concentrated hydrochloric acid; after cooling, alkalisation is effected with 6N sodium hydroxide solution, followed by extraction with ether. The oily residue obtained after the solvent has been distilled off is dissolved in 100 ml of ethanol and hydrogenated with platinum/hydrogen. After filtration from the catalyst and the solvent has been distilled off, a yellowish oil (4.8 g) is obtained.

Example 75

1 - acetyl - 2 - benzylpyrrolidine

According to the method of working described in Example 65, from 6 g of 2-benzylpyrrolidine, 4.14 g of triethylamine and 2.65 g of acetyl chloride there are obtained 5.8 g of a viscous oil.

Example 76

1 - acetyl - 2 - (4 - nitrobenzyl) - pyrrolidine

5.0 g of 1 - acetyl - 2 - benzylpyrrolidine are dissolved at 0° in 25 ml of concentrated sulphuric acid; at this temperature there are added dropwise, with stirring, 20 ml of concentrated nitric acid. After warming to room temperature, the mixture is poured into 200 ml of ice water and extraction is effected with ether. After drying over sodium sulphate, treatment of the solution with activated charcoal and the solvent has been distilled off, the product remains behind as reddish oil.

Example 77

1 - acetyl - 2 - (4 - aminobenzyl) - pyrrolidine

3.3 g of 1 - acetyl - 2 - (4 - nitrobenzyl) - pyrrolidine are hydrogenated with platinum/hydrogen in ethanol. Filtration from the catalyst is effected and the filtrate is concentrated to a yellowish liquid.

Example 78

1 - ethyl - 2 - (4 - aminobenzyl) - pyrrolidine

According to the method of working described in Example 66, from 2.5 g of 1 - acetyl - 2 - (4 - aminobenzyl) - pyrrolidine and 0.44 g of lithium aluminium hydride there are obtained 1.3 g of viscous light-brown oil (55%).

Example 79

2 - benzyl - 1 - cyclopropylcarbonylpyrrolidine

According to the method of working described in Example 65, from 6 g of 2-benzylpyrrolidine, 4.14 g of triethylamine and 4.26 g of cyclopropanecarboxylic acid chloride there are obtained 5.2 g of an oil of b.p. 120—126° at 0.005 mm Hg.

Example 80

2 - benzyl - 1 - cyclopropylmethylpyrrolidine

According to the method of working described in Example 66, from 5.0 g of 2 - benzyl - 1 - cyclopropylcarbonylpyrrolidine and 0.84 g of lithium aluminium hydride there are obtained 3.2 g of a colourless liquid of b.p. 100—105° at 0.008 mm Hg.

Example 81

1 - cyclopropylmethyl - 2 - (4 - nitrobenzyl) - pyrrolidine

According to the method of working described in Example 49, from 2 - benzyl - 1 - cyclopropylmethylpyrrolidine the title compound is obtained as red oil.

Example 82

2 - (4 - acetylaminobenzyl) - 1 - methylpyrrolidine

To a solution of 1.9 g of 2 - (4 - aminobenzyl) - 1 - methylpyrrolidine and 1 g of triethylamine in 10 ml of benzene there is added dropwise a solution of 0.78 g of acetyl chloride in 5 ml of benzene. After one hour, concentration is effected, followed by taking up with water and ether; the organic phase is collected and concentrated to a yellowish oil.

Example 83

2 - dimethylamino - 2 - methoxy - 1 - methylpyrrolidine

To 12.65 g of sodium methylate, suspended in 120 ml of absolute ether there are added dropwise at room temperature, with stirring, 50.0 g of 2 - dimethylamino - 1 - methyl - 1 - pyrrolinium - methylsulphate and boiling under reflux is then effected for 1 hour; after cooling, filtration from the precipitated salt is effected and the filtrate, after the ether has been drawn off, is distilled in a vacuum.

9.0 g of a liquid, with a very marked tendency to decomposition, of b.p. 45—47° at 11 mm Hg are obtained.

Example 84

2 - [1' - cyano - 4 - chlorobenzylidene] - 1 - methylpyrrolidine

7.9 g of 2 - dimethylamino - 2 - methoxy - 1 - methylpyrrolidine and 7.05 g of 4-chlorobenzylcyanide in 30 ml of benzene are stirred for 3 hours at 45°, freed from the solvent by distillation and the dark-brown crystallising residue is taken up with 10 ml of isopropanol and filtered. 2.5 g of yellowish crystals of m.p. 68—71°.

Example 85

2 - [1' - cyano) - 4 - nitrobenzylidene] - 1 - methylpyrrolidine

29.9 g of 2,2 - diethoxy - 1 - methylpyrrolidine and 28 g of 4-nitrophenylacetonitrile in 80 ml of benzene are stirred for one hour at room temperature, the solvent is distilled off in a vacuum and the crystalline residue is recrystallised from ethanol/ether. After concentration of the mother liquor, 29.5 g (70% of theory) of dark-brown shiny crystals of m.p. 67° are obtained.

Example 86

1 - methyl - 2 - (3 - pivaloyloxybenzyl) - pyrrolidine

380 mg of 2 - (3 - hydroxybenzyl) - 1 - methylpyrrolidine are stirred at 100° for 2.5 hours with 480 mg of pivaloyl chloride in 5 ml of absolute pyridine and poured into 50 ml of ice water; 20 ml of saturated sodium carbonate solution are added and extraction is effected with ether. The ether extract is dried over sodium sulphate, the solvent is distilled off and the residue is distilled in a high vacuum. 320 mg (58% of theory) of colourless liquid of b.p. 95—100° at 0.002 mm Hg.

Example 87

2 - (α - cyano - 4 - aminobenzylidene) - 1 - methylpyrrolidine

10 g of 2 - (α - cyano - 4 - nitrobenzylidene) - 1 - methylpyrrolidine are dissolved in ethanol and reduced with platinum/hydrogen. After completion of hydrogen uptake, filtration from the catalyst is effected, the solvent is distilled off

and the residue is recrystallised from 50 ml of ethanol. 5.5 g of light-brown crystals of m.p. 116—118° are obtained.

Example 88

2 - (4 - aminobenzyl) - 1 - methylpyrrolidine

According to the method of working described in Example 46, variant a, from 3.3 g of 2 - (α - cyano - 4 - aminobenzylidene) - 1 - methylpyrrolidine there are obtained 2.2 g of the title compound of m.p. 59—60°.

Example 89

2 - (4 - chlorobenzyl) - 1 - [3 - (4 - fluorobenzyl) - propyl] - pyrrolidine

4 g of 2 - (4 - chlorobenzyl) - pyrrolidine, 6.8 g of ω - chloro - 4 - fluorobutyrophenone, 4.2 g of potassium carbonate and 20 ml of methyl ethyl ketone are boiled under reflux for 68 hours; after cooling, 50 ml of water and 50 ml of ether are added, the ether phase is collected and drying over sodium sulphate is effected followed by concentration to a brown oil which is distilled in a high vacuum. 2.0 g of viscous light-brown oil of b.p. 188—192° at 0.02 mm Hg are obtained.

Example 90

2 - (4 - chlorobenzyl) - 1 - [4 - (4 - fluorophenyl) - butyl] - pyrrolidine

0.8 g of 2 - (4 - chlorobenzyl) - 1 - [3 - (4 - fluorobenzoyl) - propyl] - pyrrolidine are heated to 170° for 2 hours with 1 ml of hydrazine hydrate, 0.5 g of potassium hydroxide and 5 ml of triglycol; after cooling, water and ether are added, the ethereal phase is dried over sodium sulphate and the solvent is distilled off. The title compound remains behind as brownish viscous oil.

Example 91

2 - (4 - chlorobenzyl) - 1 - [4 - (4 - fluorophenyl) - 4 - hydroxybutyl] - pyrrolidine

0.8 g of 2 - (4 - chlorobenzyl) - 1 - [3 - (4 - fluorobenzoyl) - propyl] - pyrrolidine is stirred at room temperature for 3 hours with 0.5 g of sodium borohydride in 8 ml of methanol/2 ml of water, concentrated, taken up with water/ether, the ethereal phase is dried over sodium sulphate and the solvent is distilled off. The title compound remains behind as light-brown viscous oil.

Example 92

2 - (4 - chlorobenzyl) - pyrrolidine

20 g of 2 - (α - cyano - 4 - chlorobenzylidene) - pyrrolidine and 50 ml of concentrated hydrochloric acid are boiled under reflux for 2.5 hours; after cooling, the mixture is adjusted to pH 5 to 6 with 6N sodium hydroxide solution, 50 ml of methanol are added and, within 20 minutes, 1.72 g of sodium borohydride are added. The pH value is kept constant by occasional dropwise addition of hydrochloric acid. Stirring is continued for 30 minutes afterwards, followed by alkalisation with sodium hydroxide solution, extraction with methylene chloride, drying of the organic phase over sodium sulphate, concentration, and distillation of the residue in a vacuum. Yield 11.12 g (63% of theory) of b.p. 80° at 0.005 mm Hg.

The hydrochloride (from methanol/ether) melts at 189—192°.

Example 93

(−) - 2 - (4 - chlorobenzyl) - pyrrolidine

To 19.57 g of 2 - (4 - chlorobenzyl) - pyrrolidine, dissolved in 200 ml of acetone, there is added a solution of 37.6 g of dibenzoyl-L-tartaric acid in 250 ml of acetone. The mixture is left to stand for 12 hours and the crystals (25.8 g) are filtered off. $[\alpha]_{589}^{20}$=−84.7° (25 mg/ml in methanol). Recrystallisation is effected from 75 ml methanol/100 ml acetone and 15.43 g of m.p. 178—179° are obtained. $[\alpha]_{589}^{20}$=−88° (25 mg/ml in methanol). 14.85 g of this salt are stirred with sodium hydroxide solution/ether until two clear phases have formed. The ether phase is collected; drying over sodium sulphate is effected, followed by concentration to a colourless oil (5.0 g) which is converted into the hydrochloride by treatment with methanol/ethereal hydrochloric acid. Yield 4.83 g of m.p. 216—218°. $[\alpha]_{589}^{20}$=−31.4° (25 mg/ml in methanol).

From the filtrate of the crystalline dibenzoyltartrate there is isolated the

dextro-rotatory enantiomer of the hydrochloride with an optical purity of 0.79. $[\alpha]_{589}^{20}$=+24.8° (25 mg/ml in methanol).

Example 94

2 - (4 - chlorobenzyl) - pyrrolidine

1.05 g of 5 - (4 - chlorobenzyl) - pyrrolidin - 2 - one and 0.2 g of lithium aluminium hydride are heated under reflux for 20 hours in 20 ml of tetrahydrofuran. Decomposition is effected with ice water; 5 ml of 6N sodium hydroxide solution are added and the base is extracted with diethyl ether. After drying over sodium sulphate, concentration is effected to give an oil (0.7 g) which is converted into the hydrochloride with methanol/ethereal hydrochloric acid; yield 580 mg.

m.p. of the hydrochloride 189—192°.

5 - (4 - chlorobenzyl) - pyrrolidin - 2 - one (m.p. 95—98°) is obtained by reacting 4-chlorobenzylcyanide with succinic acid diethyl ester in the presence of sodium ethanolate, boiling the condensation product, without further purification, with a mixture of glacial acetic acid/semi-concentrated hydrochloric acid for 20 hours under reflux, converting with hydroxylamine the thus obtained 5 - (4 - chlorophenyl) - 4 - oxo - pentanoic acid (m.p. 91—93°) into 5 - (4 - chlorophenyl) - 4 - hydroxyiminopentanoic acid (m.p. 116—117°), hydrogenated the latter with platinum/activated charcoal/hydrogen in acetic acid to give 5 - (4 - chlorophenyl) - 4 - aminopentanoic acid which is cyclised to give the stated pyrrolidinone through boiling in dioxan.

Example 95

2 - (4 - aminobenzyl) - 1 - methylpyrrolidine

2.04 g of 5 - (4 - aminobenzyl) - 1 - methylpyrrolidin - 2 - one and 0.7 g of lithium aluminium hydride are boiled under reflux for 20 hours in 20 ml of tetrahydrofuran; decomposition is effected with ice water and, after addition of 10 ml of 6N sodium hydroxide solution, extraction is effected with diethyl ether. After drying over sodium sulphate, the ether extract is concentrated and the base thus obtained is converted into the dihydrochloride with methanol/ethereal hydrochloric acid. m.p. (from methanol/ether):>242° (decomp.).

5 - (4 - aminobenzyl) - 1 - methylpyrrolidine is obtained by nitrating 5 - benzyl - 1 - methylpyrrolidin - 2 - one with nitric acid/sulphuric acid, pouring on to ice water, extracting with methylene chloride, evaporating the extract and hydrogenating without further purification the thus obtained 1 - methyl - 5 - (4 - nitrobenzyl) - pyrrolidin - 2 - one with platinum/hydrogen.

The preparation of 1 - methyl - 5 - (4 - nitrobenzyl) - pyrrolidin - 2 - one is alternatively effected by reaction of 5 - benzylpyrrolidin - 2 - one with methyl iodide in the presence of potassium carbonate in ethyl methyl ketone with nitration of the isolated 5 - benzyl - 1 - methylpyrrolidin - 2 - one with nitric acid/sulphuric acid.

Example 96

2 - (2,4 - dinitrobenzylidene) - 1 - methylpyrrolidine

7.0 g of 2,4-dinitrotoluene and 9.65 g of 2,2 - diethoxy - 1 - methylpyrrolidine are stirred for 5 hours at 40° in 50 ml of benzene. The mixture is allowed to cool, the precipitate is filtered off and washing is effected with a little benzene and hexane. Yield 3.5 g of black-violet crystals of m.p. 188—190°.

Example 97

2 - (2,4 - diaminobenzyl) - 1 - methylpyrrolidine

3.0 g of 2 - (2,4 - dinitrobenzylidene) - 1 - methylpyrrolidine are hydrogenated in 50 ml of ethanol with platinum/hydrogen. Filtration from the catalyst is effected, followed by concentration to give a yellowish viscous oil.

Example 98

2 - (4 - chlorobenzyl) - 1 - methylpyrrolidine

99 g of 1-methylpyrrolidinone-2 and 126 g of dimethylsulfate are stirred for 3 hours at 80°. After cooling down a solution of 150 ml of dimethylamine in 150 ml of benzene is dropped into the mixture within 30 minutes while cooling with ice. The mixture is refluxed for 3 hours, 121 g of benzylcyanide are added and a solution of 23 g of sodium in 500 ml of ethanol is dropped into the mixture within 3 hours at 90°. The solution is refluxed for another 1-1/2 hours, then the main part of the solvent is evaporated, the residue is dissolved in 400 ml of water and extracted with

dichloromethane. The organic phase is concentrated and heated at reflux with 250 ml of concentrated hydrochloric acid. The solution is then made basic with 6N sodium hydroxide and extracted with dichloromethane. The extract is concentrated to a light yellow oil which after dissolution in 250 ml of ethanol is hydrogenated over platinum on charcoal. The catalyst is filtered off, the filtrate is concentrated and the residue distilled in vacuo to give 85 g of the wanted product, b.p. 73—78° at 0.005 mm Hg.

Example 99

2 - (4 - chlorobenzyl) - pyrrolidine

A solution of 10 mmol of n-butyllithium in n-hexane is added to a solution of 1.01 g of diisopropylamine in 100 ml of tetrahydrofuran at −78° under argon. The mixture is stirred for 5 minutes at room temperature and then cooled down again to −78°. A solution of 1.0 g of 1-nitrosopyrrolidine is added and stirring is continued for 1 hour. Then, 4.1 g of 4-chlorobenzyl bromide in a small amount of diethyl ether are added. After stirring for another 5 hours at −78° 5 ml of glacial acetic acid are added and the mixture is warmed up to room temperature, poured onto 50 ml of dichloromethane/50 ml of a saturated sodium chloride solution and well agitated. The dichloromethane phase is collected and the solvent is driven off. The remaining brown oil is dissolved in 50 ml of benzene, hydrogen chloride is passed into the solution for 15 minutes followed by passing through argon. The solution is rendered alkaline with aqueous sodium hydroxide and the crude pyrrolidine is extracted with diethyl ether. After removal of the solvent the remaining base is converted into the hydrochloride with methanol/ethereal hydrochloric acid.

One obtains 1.28 g (55% of theory) of m.p. 189—192° from methanol/diethyl ether).

Example 100

2 - (4 - methoxybenzyl) - pyrrolidine

A solution of 10 mmol of n-butyllithium in n-hexane is added to a solution of 1.01 g of diisopropylamine in 100 ml of tetrahydrofuran at −78° and passing argon. The mixture is stirred for 5 minutes at room temperature and then cooled again down to −78°. A solution of 1.0 g of 1-nitrosopyrrolidine is added and stirred for 1 hour. Then, 4.0 g of 4-methoxybenzyl bromide in a small amount of diethyl ether are added. After stirring for another 5 hours at −78° 5 ml of glacial acetic acid are added. The mixture is warmed up to room temperature, poured onto 50 ml of dichloromethane/50 ml of a saturated sodium chloride solution and well stirred. The dichloromethane phase is collected and the solvent is distilled off. The oily residue is dissolved in 50 ml of methanol. After addition of 2 g of Raney nickel freshly prepared, hydrogen is passed into the solution for 5 hours whilst stirring. The catalyst is filtered off and washed with methanol, the methanolic filtrate is concentrated. By treating the residue with ethanol/ethereal hydrochloric acid one obtains the hydrochloride of the title compound; m.p. 140—142°.

Example 101

2 - (4 - hydroxybenzyl) - 1 - methylpyrrolidine

3.5 g of α - (4 - methoxyphenyl) - 1 - methylpyrrolidinyl - 2 - methanol, 2 g of red phosphorus and 50 ml of 67% strength solution of hydroiodic acid are refluxed for 12 hours. Filtration and distillation of the filtrate in a vacuum removes most of the acid. The residue is taken up with diluted sodium hydroxide solution and extracted with dichloromethane. The organic phase is dried over sodium sulphate and concentrated. Recrystallisation from ethanol/charcoal yields 1.4 g of the title compound of m.p. 160—162°.

Example 102

Formula for 100 Litres (Ampoules)

1. 2 - (4 - chlorobenzyl) - 1 - methylpyrrolidine	2.500 kg
2. mannitol	4.000 kg
3. double-distilled water	ad 100 litres

1 is dissolved in 80 litres of water with addition of the equivalent amount of hydrochloric acid, then 2 is added. The solution is adjusted to a pH of 7.0±0.5 and the volume is made up with the remainder of the water. The solution is sterilised by filtration via a filter and filled in 2 ml ampoules under sterile conditions.

Example 103
Formula for Tablets

1. 2 - (4 - chlorobenzyl) - pyrrolidine hydrochloride	10.0 kg
2. glutamic acid	5.0 kg
3. maize starch	38.0 kg
4. lactose	37.0 kg
5. "Aerosil"	1.5 kg
6. sodium laurylsulphate	2.0 kg
7. gelatin	2.5 kg
8. glycerol	0.5 kg
9. talc	2.5 kg
10. magnesium stearate	1.0 kg

2 is mixed with 5 kg of 4 and finely ground. This mixture is mixed with 1 and 30 kg of 3, the remainder of 4, 5 and 6 and sieved. This mixture is moistened with a solution of 7 and 8 in 35 litres of water and forced through a sieve of mesh size 1.25 mm. After drying, the granulate is well mixed with the remainder of 3, 9 and 10 and compressed into tablets of 200 mg each.

Example 104

1. 2 - (4 - aminobenzyl) - 1 - methylpyrrolidine dihydrochloride	30.0 kg
2. cellulose "Rehocel"	8.5 kg
3. lactose	25.0 kg
4. maize starch	22.2 kg
5. Kollidon 25	3.0 kg
6. carboxymethylcellulose (Primojel)	8.5 kg
7. talc	2.5 kg
8. magnesium stearate	0.3 kg

1, 2, 3, 4 are mixed, moistened with 5 (dissolved in 15 litres of water) and granulated. Thereafter, preliminary drying is effected in a drying chamber at 50° and the material is subsequently passed through a sieve. The granulate is dried to a relative moistness of 45—50% and, after addition of 6, 7 and 8 and careful mixing, is compressed into tablets of 100 mg weight.

Example 105
Formula for Tablets

1. 2 - (3 - hydroxybenzyl) - 1 - methylpyrrolidine fumarate	25.0 kg
2. cellulose ("Rehocel")	8.5 kg
3. lactose	30.0 kg
4. maize starch	22.2 kg
5. Kollidon 25	3.0 kg
6. carboxymethylcellulose (Primojel)	8.5 kg
7. talc	2.5 kg
8. magnesium stearate	0.3 kg

1, 2, 3, 4 are mixed, moistened with 5 (dissolved in 15 litres of water) and granulated. Thereafter, preliminary drying is effected in a drying chamber at 50° and the material is subsequently passed through a sieve. The granulate is dried to a relative moistness of 45—50% and, after addition of 6, 7 and 8 and careful mixing, is compressed into tablets of 100 mg weight.

Pharmacological Investigations

The pharmacological properties of the compounds according to the invention are clearly demonstrable on albino mice and albino rats, e.g. central stimulation, reserpine antagonism, analgesic action, anticataleptic effect and anti-hypertensive activity.

In the following Tables the compounds investigated are identified by a serial number, which is assigned as follows:

Serial No.	Name of compound
1	2 - (3 - methoxybenzyl) - 1 - methylpyrrolidine
2	2 - (4 - chlorobenzyl) - 1 - methylpyrrolidine
3	2 - (4 - aminobenzyl) - 1 - methylpyrrolidine
4	2 - (2 - methoxybenzyl) - 1 - methylpyrrolidine
5	2 - (4 - chlorobenzyl) - 1 - isopropylpyrrolidine
6	2 - (4 - chlorobenzyl) - pyrrolidine
7	2 - (3 - hydroxybenzyl) - 1 - methylpyrrolidine
8	2 - (4 - fluorobenzyl) - 1 - methylpyrrolidine
9	2 - (4 - bromobenzyl) - 1 - methylpyrrolidine
10	2 - (4 - chlorobenzyl) - 1 - cyclopropylmethylpyrrolidine
11	2 - (4 - methoxybenzyl) - pyrrolidine
12	2 - (4 - hydroxybenzyl) - 1 - methylpyrrolidine
13	1 - methyl - 2 - (4 - nitrobenzyl) - pyrrolidine
14	2 - (3,4 - dimethoxybenzyl) - 1 - methylpyrrolidine
15	2 - (2,4 - dichlorobenzyl) - 1 - methylpyrrolidine
16	1 - methyl - 2 - (3 - methylbenzyl) - pyrrolidine
17	2 - (3 - chlorobenzyl) - 1 - methylpyrrolidine
18	2 - (4 - methoxybenzyl) - 1 - methylpyrrolidine
19	2 - (3,4 - dihydroxybenzyl) - 1 - methylpyrrolidine
20	1 - allyl - 2 - (4 - chlorobenzyl) - pyrrolidine
21	1 - methyl - 2 - (3,4,5 - trimethoxybenzyl) - pyrrolidine
22	2 - (4 - chlorobenzyl) - 1 - hexylpyrrolidine
23	2 - (2 - chlorobenzyl) - 1 - methylpyrrolidine
24	1 - methyl - 2 - (3,4,5 - trihydroxybenzyl) - pyrrolidine

Compounds according to the invention are distinguished by central stimulation, as finds its expression in an increase of vigilance and excitability; in rarer cases, also in mild promotion of motor activity. The results of the behaviour investigations are reproduced in Table I.

TABLE I

Increase of vigilance and excitability from			Additional increase of activity from		
Serial No.	mg/kg orally	Intensity	Serial No.	mg/kg orally	Intensity
1	5	++	5	25	+
2	5	++	10	100	+
3	5	++	22	100	+
4	5	++	9	200	+
5	5	++			
6	10	+(+)			
7	25	+			
8	5	+(+)			
9	25	+			
10	25	+			
11	25	+			
12	25	+			
13	50	+			
14	50	+			
15	50	+			
16	50	(+)			
17	50	(+)			
18	50	(+)			
19	100	(+)			
20	50	(+)			
21	50	(+)			
22	30	(+)			
23	5	(+)*			

Intensity scale:
++ greatly increased
+(+) very distinctly increased
+ distinctly increased
(+) mildly increased
* decrease from 50 mg/kg orally

Among the compounds according to the invention, some have a particularly strong reserpine-antagonistic activity. This antagonism is demonstrable in the case of prophylactic and therapeutic administration. In Table II the ED_{50} values according to investigations on the albino mouse are reproduced.

TABLE II

a) Prophylactic Administration to the Mouse

Serial No.	Abolition of ptosis [mg/kg orally]	Promotion of drive [mg/kg orally]
3	10	12
6	28	10
1	25	25
19	50	50
16	75	50
7	80	55
15	>100	50
5	(100)	65
10	(100)	70
9	150	Ø

b) Therapeutic Administration to the Mouse

Serial No.	Abolition of ptosis [mg/kg orally]	Promotion of drive [mg/kg orally]
3	18	37
7	25	30
1	50	75
5	75	75
16	25	(100)
11	90	90
4	80	100
17	(75)	75
13	(100)	60
10	(100)	85

For compounds according to the invention, analgesic effects can be evidenced in various analgesic models on the albino mouse.

In Table III the ED_{50} values calculated from the dose effect curves are reproduced.

TABLE III

a) Hot plate test

Serial No.	[mg/kg orally
4	2.0
6	2.5
22	3.5
18	5
2	5
17	20
13	25
11	25
14	35
3	50
19	50
23	50
21	50

b) Tail flick test

Serial No.	[mg/kg orally]
5	25
3	50
9	50
19	50
22	70
11	80

c) Writhing test (acetic acid)

Serial No.	[mg/kg orally]
6	35
18	45
3	50
4	60

Compounds according to the invention have prophylactic activities against the formation of a catalepsy caused by haloperidol. In Table IV the ED_{50} values according to investigations on the albino mouse are reproduced.

TABLE IV

Serial No.	[mg/kg orally]
6	7
2	24
21	25
5	25—50
20	65
3	80

Compounds according to the invention cause a reduction of blood pressure in the anaesthetised normotonic albino rat. In Table V the maximum lowering of blood pressure [in mm Hg] in the range of the first 5 minutes and 60 minutes after application in the case of a dose of 50 μmoles/kg intravenously is reproduced.

TABLE V

Serial No.	Lowering of blood pressure [mm Hg] Max. [5 min. after application]	60 min. after application
19	35	28**
23	51	39
7	40	32
4	40	38
3	38	19
6	36	18
16	28	10
2	27	15
1	26	15
24	23	22
5	15	12

** in the case of application of 10 μmoles/kg.

The determination of the pharmacological properties was effected according to the following methods:

1. Behaviour

For the observation of the behaviour of albino mice, in each instance 5 animals were kept in a "Makrolon" cage, Type II. A comparative assessment vis-à-vis untreated controls was made. Vigilance and increase of motor activity are assessed from the behaviour of the undisturbed mice; the increased excitability is assessed from the reaction to outer stimuli, such as noise and contact in comparison with the reaction of the control animals.

2. Reserpine Antagonism

Subcutaneous application of 2 mg/kg of reserpine causes ptosis in albino mice in the course of several hours; also, the normal movement activity of the animal (drive) is considerably inhibited. The intensity of both symptoms is graded by a points system: 0—1—2—3 by which the degree of the effect (from no effect to complete ptosis, and from no inhibition to complete inhibition of drive) is reflected. These experiments may be carried out both under prophylactic and under therapeutic application of the test substances. The substances tested antagonise the symptoms in dependence on the dose. The ED_{50} of the antagonistic effect in comparison with the daily control is evaluated. Literature: Reserpin-Antriebshemmung ("Reserpine Drive Inhibition") [Sulser, Bickel, Brodie, 1961 Med. Exp. 5, 454]; Reserpin-Ptosis [Domenjoz and Theobald (1959), Arch. Int. Pharmacodyn. 120/450].

3. Analgesia

a) Hot-plate test: female albino mice are placed on a 50°C hot plate and the reaction time until pawls are licked is recorded with a stopwatch. Normal values lie in the range of 7—8 seconds. The substances tested cause delayed reaction to the heat stimulus, i.e. a reduced sensitivity to heat pain. The dose which prolongs the

reaction time by 50% was determined. Literature: Eddy, N.B. and Leimbach, D. (1953) J. Pharmacol. Exp. Ther. 107, 385.

b) Tail flick test: to female albino mice there is applied a thermal pain on the tail root with a focused heat ray and the time until the tail is drawn away is recorded with a stopwatch. Normally the time lies in the range of 4—5 seconds. The substances cause delayed reaction to the thermal pain, i.e. a reduced reaction to thermal pain. The dose which prolongs the reaction time by 50% was determined. Literature: D'Amour, F. E. and Smith D. L. (1941) J. Pharmacol. Exp. Ther. 72, 74.

c) Writhing test (acetic acid writhing): intraperitoneal injection of 0.2 ml/20 g mouse of an 0.75% strength acetic acid solution induces an albino mice a typical syndrome, called writhing, proceeding over the body with dorsal flection. These writhings occurring in the course of the first half hour after application are counted in the range of 5—20 minutes after application. The substances tested cause a lessening of the number of writhing syndromes. The dose which reduces the writhings by 50% with reference to the daily control is determined. Literature: Koster, Andersen de Beer (1959) Fed. Proc. 18, 42.

4. Haloperidol Antagonism

Subcutaneous application of haloperidol (7.5 mg/kg) causes catalepsy in albino mice. The cataleptic behaviour of the animals is tested by placing the animals on a wire cradle bridge for 30 seconds. The substances tested prevent, in manner depending on the dose, the occurrence of catalepsy after application of haloperidol. The dose which inhibits the occurrence of catalepsy in 50% of the animals is determined. Literature: L. Julou, M. C. Bardone, R. Ducrot, B. Lafforgue and G. Loiseau in Neuro-Psycho-Pharmacology, Ed. H. Brill et al., Exerpta Medica Foundation Internat. Congress Series No. 129,293—303 (1967).

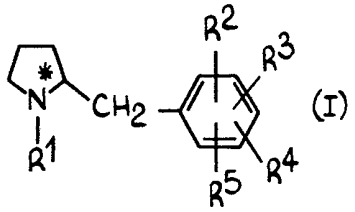
5. Blood Pressure Determinations

The substances are applied intraveneously to normotone albino rats (Sprague Dawley; male) which have been anaesthetised with chloralose (80 mg/kg intraperitoneally). The blood pressure measurement is effected in the A. carotis dexter by means of Statham pressure recorder; the measurement of the heart frequency was effected with EKA pulse rate meter. The body temperature is kept constant to 37.5±0.2°C through warming with an incandescent lamp which is controlled via a rectal temperature sensor. Registration is effected continuously over one hour p.a. The maximum of the effect within the first 5 minutes and of the effect after 60 minutes are determined.

The words "Amberlite", "Aerosil", Rehocel" and "Makrolon" are Registered Trade Marks.

WHAT WE CLAIM IS:—

1. Substituted 2-benzylpyrrolidines of the general formula I



wherein

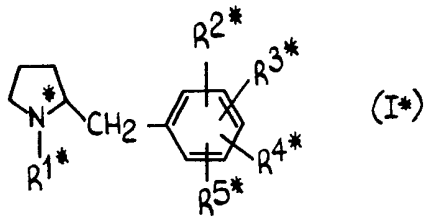
R^1 denotes a hydrogen atom, a straight-chain or branched aliphatic or alicyclic hydrocarbon radical, a cycloalkylalkyl group or an optionally substituted aralkyl or aroylalkyl group,

R^2 denotes a halogen atom, an alkyl group, a hydroxyl group, an alkoxy group, an acyloxy group, an amino group which may be substituted, a nitro group or a phenyl group which may be substituted,

R^3, R^4 and R^5 are the same or different and denote a hydrogen atom, a halogen atom, an alkyl group, a hydroxyl group, an alkoxy group, an acyloxy group, an optionally substituted amino group, a nitro group or an optionally substituted phenyl group,

their quaternary alkylpyrrolidinium compounds and their acid addition salts.

2. Substituted 2-benzylpyrrolidines of the general formula I*



(I*)

wherein

R^{1*} denotes a hydrogen atom, a straight-chain or branched aliphatic hydrocarbon radical with 1 to 5 carbon atoms, a cycloalkylalkyl group with 1 or 2 carbon atoms in the alkyl radical and 3 to 5 carbon atoms in the cycloalkyl radical, or an optionally mono-substituted phenylalkyl group with 1 to 4 carbon atoms in the alkyl radical,

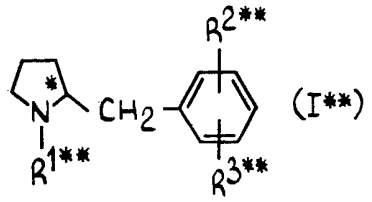
R^{2*} denotes a halogen atom, a hydroxyl group, an alkyl group with 1 to 4 carbon atoms, an alkoxy group with 1 to 4 carbon atoms, an alkanoyloxy group with 2 to 5 carbon atoms, an amino group, a dialkylamino group with 1 or 2 carbon atoms per alkyl radical or a nitro group, or a phenyl group which may be substituted in p-position,

R^{3*}, R^{4*} and R^{5*} denote a hydrogen atom, a halogen atom, a hydroxyl group, an alkyl group with 1 to 4 carbon atoms, an alkoxy group with 1 to 4 carbon atoms, an alkanoyloxy group with 2 to 5 carbon atoms, an amino group, a dialkylamino group with 1 or 2 carbon atoms per alkyl radical or a nitro group, and at least one of the substituents in 2- or 6-position of the benzyl group is a hydrogen atom,

their quaternary (C_1—C_4) alkylpyrrolidinium compounds and their acid addition salts.

3. Compounds according to Claim 2, in which R^{1*}, R^{2*}, R^{3*}, R^{4*} and R^{5*} have the meaning stated above, and at least one, preferably two, of the substituents R^{3*}, R^{4*} or R^{5*} and at least one of the substituents in 2- or 6-position of the benzyl group denote a hydrogen atom, and their quaternary (C_1—C_4) alkylpyrrolidinium compounds and their pharmacologically compatible acid addition salts.

4. Substituted 2-benzylpyrrolidines of the general formula I**



(I**)

wherein

R^{1**} denotes a hydrogen atom, a straight-chain alkyl radical with 1 to 3 carbon atoms, a branched alkyl radical with 3 to 5 carbon atoms, a cycloalkylmethyl radical with 3 to 5 carbon atoms in the cycloalkyl group or a benzyl radical which may be substituted in p-position by halogen, methyl or methoxy,

R^{2**} denotes a halogen atom, a hydroxyl group, a methoxy group, an amino group or a nitro group,

R^{3**} denotes a hydrogen atom, a halogen atom, a hydroxyl group, a methoxy group, an amino group or a nitro group, the substituents R^{2**} and R^{3**} preferably being in two positions selected from the 2, 3 and 4 positions,

and their methylpyrrolidinium compounds and their pharmacologically compatible acid addition salts.

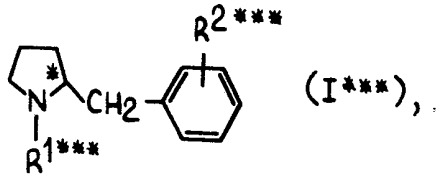
5. Compounds according to Claim 4, in which

R^{1**} denotes a hydrogen atom, a methyl group, an isopropyl group, a tert.-butyl group, a cyclopropylmethyl group or a benzyl group,

R^{2**} and R^{3**} have the meaning stated above,

and their pharmacologically compatible acid addition salts.

6. Substituted 2-benzylpyrrolidines of the general formula I***



wherein

R^{1***} denotes a hydrogen atom, a methyl group, an isopropyl group or a cyclopropylmethyl group and,

R^{2***} represents a 2-, 3- or 4-positioned, fluorine, chlorine, hydroxy, methoxy or amino substituent,

and their pharmacologically compatible acid addition salts.

7. Compounds according to Claim 6 in which R^{1***} and R^{2***} have the meaning stated above and R^{2***} is in the 3- or 4-position, and their pharmacologically compatible acid addition salts.

8. 2 - (2 - chlorobenzyl) - 1 - methylpyrrolidine and its pharmacologically compatible acid addition salts.

9. 2 - (4 - chlorobenzyl) - 1 - methylpyrrolidine and its pharmacologically compatible acid addition salts.

10. 2 - (3 - methoxybenzyl) - 1 - methylpyrrolidine and its pharmacologically compatible acid addition salts.

11. 2 - (3 - hydroxybenzyl) - 1 - methylpyrrolidine and its pharmacologically compatible acid addition salts.

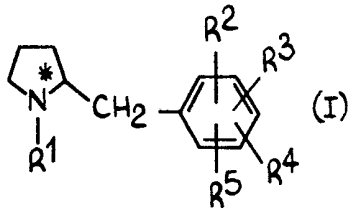
12. 2 - (4 - aminobenzyl) - 1 - methylpyrrolidine and its pharmacologically compatible acid addition salts.

13. 2 - (4 - chlorobenzyl) - pyrrolidine and its pharmacologically compatible acid addition salts.

14. 2 - (3 - chlorobenzyl) - 1 - methylpyrrolidine and its pharmacologically compatible acid addition salts.

15. 2 - (2 - methoxybenzyl) - 1 - methylpyrrolidine and its pharmacologically compatible acid addition salts.

16. Pharmaceutical compositions containing as active ingredient at least one 2-benzylpyrrolidine of the general formula I



wherein

R^1 denotes a hydrogen atom, a straight-chain or branched aliphatic or alicyclic hydrogen radical, a cycloalkylalkyl group or an optionally substituted aralkyl or aroylalkyl group,

R^2, R^3, R^4 and R^5 are the same or different and denote a hydrogen atom, a halogen atom, an alkyl group, a hydroxyl group, an alkoxy group, an acyloxy group, an optionally substituted amino group, a nitro group, or an optionally substituted phenyl group, their quaternary alkylpyrrolidinium compounds and/or their pharmacologically compatible acid addition salts, in admixture with one or more solid or liquid pharmaceutically acceptable inert carriers.

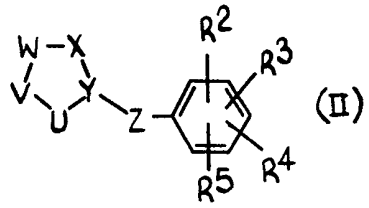
17. Pharmaceutical compositions containing compounds according to one of Claims 2 to 15 in admixture with one or more solid or liquid pharmaceutically acceptable inert carriers.

18. Use of the 2-benzylpyrrolidines I as defined in Claim 16 or their embodiments I*, I** or I*** as defined in Claims 2, 4 and 6 and/or their pharmacologically compatible acid addition salts in the treatment of mammals excluding humans for troubles of the central nervous system, of pathological changes of blood pressure and/or of pain states.

19. A process for the preparation of substituted 2-benzylpyrrolidines of the

general formula I, where R^2, R^3, R^4 and R^5 have the same meaning as in Claim 1, characterised in that

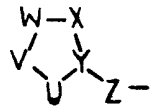
a) a substituted 2-benzylpyrrolidine of the general formula II



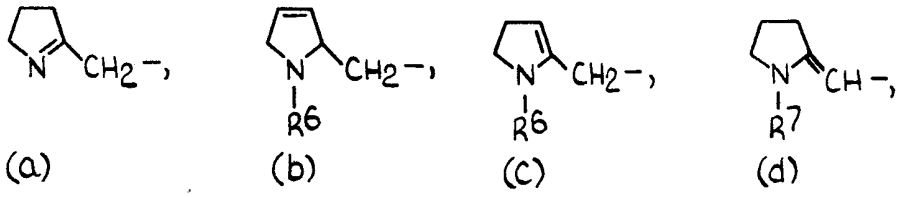
(II)

wherein

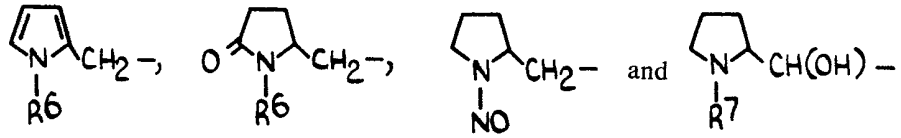
R^2, R^3, R^4 and R^5 have the meaning stated above and



denotes one of the groupings



(a) (b) (c) (d)



(e) (f) (g) and (h)

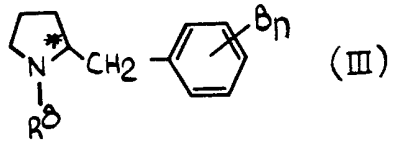
wherein

R^6 represents a hydrogen atom, a straight-chain or branched aliphatic or alicyclic hydrocarbon radical, a cycloalkylalkyl radical or an optionally substituted aralkyl or aroyloalkyl group and

R^7 represents a straight-chain or branched aliphatic or alicyclic hydrocarbon radical, a cycloalkylalkyl radical or an optionally substituted aralkyl or aroylalkyl group,

is reduced and, where appropriate, subsequently N-alkylated or N-debenzylated and/or functionalised as herein defined and/or the free base obtained or its acid addition salts are converted into one another in the usual manner or

b) a 2-benzylpyrrolidine of the general formula III



(III)

wherein

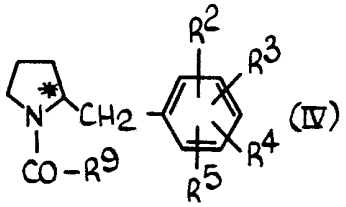
R^8 denotes a hydrogen atom, a straight-chain or branched aliphatic or alicyclic hydrocarbon radical or a cycloalkylalkyl radical,

B denotes a hydrogen atom or a precursor of a functional group, and

n denotes a whole number from 1 to 4,

is functionalised as herein defined and, where appropriate, subsequently N-alkylated or N-debenzylated and/or the obtained free base or its acid addition salts are converted into one another in the usual manner or

c) an N - acyl - 2 - benzylpyrrolidine of the general formula IV



(IV)

wherein

R^2, R^3, R^4 and R^5 are the same or different and denote a hydrogen atom, a halogen atom, an alkyl group, a hydroxyl group, an alkoxy group, an optionally substituted amino group or an optionally substituted phenyl group,

R^9 denotes a straight-chain or branched aliphatic or alicyclic hydrocarbon radical, a cycloalkyalkyl radical, an optionally substituted phenyl radical or an optionally substituted phenylalkyl radical is reduced and, where appropriate, subsequently functionalised and/or N-alkylated or N-debenzylated and/or the base obtained or its acid addition salts are converted into one another in the usual manner.

20. A process for the preparation of substituted 2-benzylpyrrolidines of the general formula I according to Claim 1 substantially as described with reference to the specific examples hereinbefore set forth.

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